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RESEARCH ARTICLE

Plasma-derived biomarkers of Alzheimer's disease and neuropsychiatric symptoms: A community-based study

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Abstract

INTRODUCTION: We examined associations between plasma-derived biomarkers of Alzheimer's disease (AD) and neuropsychiatric symptoms (NPS) in community-dwelling older adults.

METHODS: Cross-sectional study involving 1005 persons ≥50 years of age (mean 74 years, 564 male, 118 cognitively impaired), who completed plasma-derived biomarker (amyloid beta 42 [Aβ42]/Aβ40, phosphorylated tau 181 [p-tau181], p-tau217, total tau [t-tau], neurofilament light [NfL]), and NPS assessment.

RESULTS: P-tau181 (odds ratio [OR] 2.06, 95% confidence interval [CI] 1.41–3.00, $p < 0.001$), p-tau217 (OR 1.70, 95% CI 1.10–2.61, $p = 0.016$), and t-tau (OR 1.44, 95% CI 1.08–1.92, $p = 0.012$) were associated with appetite change. We also found that p-tau181 and p-tau217 were associated with increased symptoms of agitation (OR 1.93, 95% CI 1.20–3.11, $p = 0.007$ and OR 2.04, 95% CI 1.21–3.42, $p = 0.007$, respectively), and disinhibition (OR 2.39, 95% CI 1.45–3.93, $p = 0.001$ and OR 2.30, 95% CI 1.33–3.98, $p = 0.003$, respectively). Aβ42/Aβ40 and NfL were not associated with NPS.

CONCLUSION: Higher plasma-derived p-tau181 and p-tau217 levels are associated with increased symptoms of appetite change, agitation, and disinhibition. These findings may support the validity of plasma tau biomarkers for predicting behavioral symptoms that often accompany cognitive impairment.

KEYWORDS
Alzheimer's disease, neuropsychiatric symptoms, plasma biomarkers

HIGHLIGHTS

- We studied 1005 community-dwelling persons aged ≥ 50 years
- Higher plasma tau levels are associated with increased neuropsychiatric symptoms
- Aβ42/Aβ40 and NfL are not associated with neuropsychiatric symptoms
- Clinicians should treat neuropsychiatric symptoms in persons with high plasma-derived tau

1 | BACKGROUND

Neuropsychiatric symptoms such as apathy and depression are risk factors for cognitive decline in older adults.[1–5] In addition, neuropsychiatric symptoms are associated with Alzheimer's disease (AD)–related pathological processes of amyloid β (Aβ), phosphorylated tau (p-tau), and neurodegeneration as measured by biomarkers. For example, we and others have reported that neuropsychiatric symptoms are associated with cerebrospinal fluid (CSF)–[6–8] and neuroimaging-derived biomarkers of AD such as Pittsburgh compound-B positron emission tomography (PiB-PET)[9–11] and tau-PET.[12,13]

In recent years, blood-based biomarkers for AD have become available in research settings and may be implemented in clinical practice in the future.[14] Indeed, one advantage of blood-based as compared to CSF- or neuroimaging-derived biomarkers is that they are less invasive and expensive, and thus potentially more feasible for use in clinical practice.[15,16] To date, the most commonly studied blood-based biomarkers of AD pathology include Aβ42 and Aβ40, p-tau, total tau (t-tau), and neurofilament light chain (NfL), with the latter two being considered as biomarkers of neurodegeneration not specific to AD.[17] Studies conducted in community samples have reported relationships between plasma-derived AD biomarkers and post-mortem neuropathology measures,[18] cognitive and neuroimaging outcomes[15,19,20] and other factors, and comorbidities such as chronic kidney disease.[15,16]

Thus far, only few studies have examined the associations between plasma-derived AD biomarkers with neuropsychiatric symptoms, and have focused mainly on depression and plasma Aβ42 or Aβ42/Aβ40. For example, a cross-sectional study in 995 homebound older adults showed that depression was associated with lower plasma Aβ42 levels and higher plasma Aβ40/Aβ42 when persons with cardiovascular disease and using antidepressant medications were not included in the analyses.[21] The same group also reported that the association between depression and plasma levels of Aβ may differ depending on apolipoprotein E (*APOE*) ε4 carrier status.[22] In a rather small study among 86 persons with normal cognition and 53 with mild cognitive impairment (MCI), a lower plasma Aβ42/Aβ40 was associated with higher mild behavioral impairment (MBI) total score (possible range: 0-60; higher score indicating higher MBI severity) and greater affective dysregulation.[23] However, studies have also failed to establish cross-sectional associations between plasma levels of Aβ42 or Aβ42/Aβ40 and depression.[24] In general, the literature can be regarded as inconsistent, partly because techniques to determine plasma-derived biomarkers were less reliable a few years ago as compared to single-molecule techniques used today.

The aim of this study was to examine the cross-sectional associations between plasma-derived AD (i.e., Aβ42/Aβ40, p-tau181, p-tau217) and neurodegeneration (i.e., t-tau and NfL) biomarkers, and various neuropsychiatric symptoms in a large representative sample of community-dwelling older adults. We hypothesized that neuropsychiatric symptoms would be associated with plasma-derived AD biomarkers (i.e., higher levels of p-tau181, p-tau217, t-tau, and NfL, and lower Aβ42/Aβ40 levels).

2 | METHODS,

2.1 | Study design and setting

We conducted a cross-sectional study derived from the population-based Mayo Clinic Study of Aging (MCSA) in Olmsted County, MN, USA. Details of the study procedures have been reported elsewhere.[25] We included 1005 persons ≥50 years of age (mean age 74 years, 564 male, 276 *APOE* ε4 carriers, 118 cognitively impaired) on whom data on plasma-derived biomarkers and neuropsychiatric symptoms were available (please refer to Figure 1). The study was approved by the

Mayo Clinic and Olmsted Medical Center institutional review boards, and written informed consent for participation was obtained from every participant.

2.2 | Cognitive evaluation

Participants underwent a face-to-face evaluation including a neurological examination, a study coordinator visit, and neuropsychological testing.[25] Briefly, the neurological evaluation comprised a neurological history review, administration of the Short Test of Mental Status,[26] and a neurological examination. The study coordinator met with the participant and a study partner, and assessed sociodemographic data, and asked questions on memory, neuropsychiatric symptoms, and activities of daily living. Neuropsychological testing was administered by a psychometrist to assess performance in four cognitive domains: memory (Auditory Verbal Learning Test,[27] Wechsler Memory Scale-Revised[28]); language (Boston Naming Test,[29] category fluency[30]); visuospatial skills (Wechsler Adult Intelligence Scale-Revised[31]); and attention/executive function (Trail-Making Test,[32] Wechsler Adult Intelligence Scale-Revised[31]). An expert consensus panel consisting of physicians, study coordinators, and neuropsychologists reviewed the results for each participant and determined whether a participant was cognitively unimpaired or had cognitive impairment (i.e., MCI or dementia). Individuals were classified as cognitively unimpaired based on normative data developed on a different sample in this community.[33,34] For MCI, the revised Mayo Clinic criteria for MCI[35,36] were used. Participants with MCI had a Clinical Dementia Rating (CDR) score of 0 or 0.5; however, the final diagnosis of MCI was based on all available data.

2.3 | Plasma-derived AD biomarkers ascertainment

The MCSA team has published its methodology on plasma-derived biomarker assessment.[16] Briefly, participants' blood is collected in-clinic after an overnight fast, and centrifuged, aliquoted, and stored at −80°C. Plasma biomarkers are measured on the Quanterix HD-1 analyzer using the Simoa Neurology 3-Plex A for t-tau, Aβ42, and Aβ40 and Simoa NF-light Advantage kits for NfL. Previous studies have reported the area under the receiver-operating characteristic curve (AUC) between 0.65 and 0.71 with the Quanterix plasma Aβ42/40 assay for prediction of amyloid positivity in the BioFinder and Alzheimer's Disease Neuroimaging Initiative (ADNI) cohorts.[37] In addition, p-tau181 and p-tau217 were measured on the Meso Scale Discovery platform using proprietary assays developed by Eli Lilly Research Laboratories.[20] We included NfL, Aβ42/Aβ40, p-tau181, p-tau217, and t-tau in the analysis for this manuscript. The values of NfL, Aβ42/Aβ40, p-tau181, p-tau217, and t-tau were standardized to a mean of 0 and a SD of 1, to allow for direct comparison of the regression coefficients.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed publications on the associations between plasma-derived biomarkers of Alzheimer's disease (AD) and neuropsychiatric symptoms. Few studies are available to date, which focused mainly on depression and plasma amyloid beta 42 (Aβ42) or Aβ42/Aβ40. Thus we examined the associations between plasma-derived biomarkers of AD and neurodegeneration with neuropsychiatric symptoms.
2. **Interpretation**: In this population-based sample of 1005 older adults ≥50 years of age, higher plasma-derived phosphorylated tau 181 (p-tau181) and p-tau217 levels are associated with increased symptoms of appetite change, agitation, and disinhibition, whereas Aβ42/Aβ40 and neurofilament light (NfL) levels were not associated with neuropsychiatric symptoms.
3. **Future directions**: If confirmed by a future longitudinal cohort study, our findings support the validity of plasma tau biomarkers for predicting behavioral symptoms that often accompany cognitive impairment.

2.4 | Measurement of neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q[38]). The NPI-Q was administered as a structured interview to an informant such as the spouse by a study coordinator and assessed the presence or absence of 12 symptoms (i.e., depression, anxiety, apathy, agitation, delusions, hallucinations, euphoria, disinhibition, irritability, aberrant motor behavior, sleep/ nighttime disturbance behavior, and eating/appetite). In addition, we created an NPI-Q severity score as continuous measure. For this score, the severity of each present symptom, rated on a 3-point scale of 1 (mild), 2 (moderate), and 3 (severe), was summed up; thus the total score can range from 0 to 36, with a higher score indicating higher neuropsychiatric symptom severity. In addition, we assessed self-reported depression and anxiety using the Beck Depression Inventory II (BDI-II[39]) and Beck Anxiety Inventory (BAI[40]), respectively. The BDI-II measures common symptoms of depression, such as feelings of guilt or loss of interest, over the preceding 2 weeks. The BAI measures common anxiety symptoms, such as nervousness or fear of losing control, over the preceding week. Both inventories are validated and consist of 21 items. The severity of each item is rated on a Likert-type scale ranging from 0 to 3, with the total score ranging from 0 to 63. A higher score indicates higher severity of depressive and anxiety symptoms, respectively. For our analyses, we used BDI-II and BAI total scores as continuous measures, as well as BDI-II score ≥13 (indicating

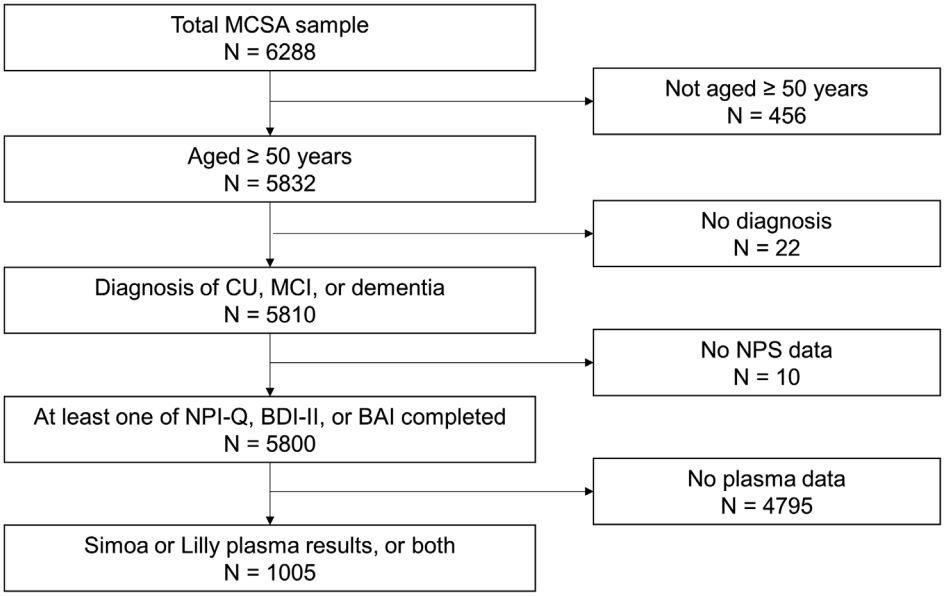

FIGURE 1 Flow chart of study participation MCSA, Mayo Clinic Study of Aging; CU, cognitively unimpaired; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms; NPI-Q, Neuropsychiatric Inventory Questionnaire; BDI-II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory.

clinical depression) and BAI score ≥10 (indicating clinical anxiety) as categorical measures.

2.5 | Assessment of confounding variables

In addition to traditional confounders (i.e., age, sex, and education), we adjusted the analyses for *APOE* ε4 genotype status, which was determined using standard methods, and medical comorbidity as assessed through the weighted Charlson index.[41]

2.6 | Statistical analysis

Descriptive statistics were calculated and presented as mean values (M) with standard deviation (SD) or frequencies (N) and percentages (%), depending on whether a variable was continuous or categorical. As the direction of causality is unknown in cross-sectional studies, we arbitrarily assigned plasma-derived biomarkers of AD and neurodegeneration (i.e., NfL, Aβ42/Aβ40, p-tau181, p-tau217, and t-tau) as presumed predictors (independent variables), and considered neuropsychiatric symptoms as the outcomes of interest (dependent variables) for the analyses. We ran logistic regression analyses to examine the association between z-score–transformed plasma-derived biomarkers of AD and neurodegeneration with presence of neuropsychiatric symptoms as assessed by the NPI-Q, BDI-II score ≥13 indicating clinical depression, and BAI score ≥10 indicating clinical anxiety (categorical measures). We computed odds ratios (ORs), 95% confidence intervals (CIs), and *p*-values. However, for delusions, euphoria/ elation, hallucinations, and motor behavior as assessed by the NPI-Q, there were not enough events to be included in the logistic regression models. In addition, we conducted linear regression analyses to examine the association between z-score–transformed plasma-derived biomarkers of AD and neurodegeneration and continuous BDI-II and BAI total scores (range for both: 0 to 63), as well as NPI-Q severity score (range: 0 to 36); and computed *β*-estimates, 95% CI, and *p*-values. Furthermore, we ran the logistic regression models only among cognitively unimpaired participants (unfortunately, it was not possible to run the models among persons with MCI/ dementia due to low numbers of neuropsychiatric symptoms), and we ran the linear regression models among both cognitively unmpaired persons and those with MCI/ dementia. All models were adjusted for age, sex, education, *APOE* ε4 carrier status, and medical comorbidity. All analyses were done using the conventional two-tailed alpha level of 0.05 and performed with SAS 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

The sample comprised 1005 adults ≥ 50 years of age. Mean (SD) age was 74.4 (9.5) years, 564 participants were male (56.1%), 276 were *APOE* ε4 carriers (27.5%), and 118 were cognitively impaired (11.7%). The most common neuropsychiatric symptoms were depression (11.1%), irritability (8.3%), nighttime behavior (6.3%), apathy (5.5%), and anxiety (5.4%). For an overview of participant demographics at baseline, please refer to Table 1.

We observed statistically significant associations between p-tau181 (OR 2.06, 95% CI 1.41–3.00, $p < 0.001$), p-tau217 (OR 1.70, 95% CI 1.10–2.61, $p = 0.016$), and t-tau (OR 1.44, 95% CI 1.08–1.92, $p = 0.012$) with appetite change. In addition, there was a statistically significant association of higher levels of *p*-tau181 and p-tau217 with

TABLE 1 Participant demographics.

Variable	Total ($N = 1005$) Mean (SD)
Age, years	74.4 (9.5)
Male sex, *N* (%)	564 (56.1)
Education, years	14.6 (2.7)
APOE ε4 carrier, *N* (%)	276 (27.5)
Charlson index	3.2 (3.1)
Cognitive impairment, *N* (%)	118 (11.7)
MCI, *N* (%)	114 (11.3)
Dementia, *N* (%)	4 (0.4)
Chronic kidney disease	85 (8.5)
NPS	
Agitation, *N* (%)	31 (3.2){49}
Anxiety, *N* (%)	52 (5.4){48}
Apathy/indifference, *N* (%)	53 (5.5){49}
Appetite/eating change, *N* (%)	44 (4.6){48}
Nighttime behavior, *N* (%)	53 (6.3){170}
Delusions, *N* (%)	6 (0.6){48}
Depression/dysphoria, *N* (%)	106 (11.1){48}
Disinhibition, *N* (%)	23 (2.4){48}
Euphoria/elation, *N* (%)	6 (0.6){48}
Hallucinations, *N* (%)	1 (0.1){48}
Irritability/lability, *N* (%)	79 (8.3){48}
Motor behavior, *N* (%)	10 (1.0){48}
NPI-Q severity score (0–36)	0.7 (1.6){49}
BDI-II total score (0–63)	4.6 (4.8){2}
BAI total score (0–63)	2.9 (4.4){1}
BDI-II ≥13, *N* (%)	69 (6.9){2}
BAI ≥10, *N* (%)	81 (8.1){1}
Plasma-derived biomarkers	
NfL	20.68 (15.34){88}
Aβ40	272.97 (77.73){118}
Aβ42	9.14 (3.21){98}
p-tau181	1.38 (1.18){3}
p-tau217	0.20 (0.25){3}
t-tau	2.70 (1.20){98}

Data presented as mean (St) unless indicated otherwise.
Abbreviations: Aβ, amyloid beta; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; MCI, mild cognitive impairment; N, number; NfL, neurofilament light; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptom; p-tau, phosphorylated tau; SD, standard deviation; t-tau, total tau.
{N}, indicates missing N.
Dementia cases: Two due to Alzheimer's disease, one not specified, and one due to head injury.

increased symptoms of agitation (p-tau181: OR 1.93, 95% CI 1.20–3.11, $p = 0.007$; p-tau217: OR 2.04, 95% CI 1.21–3.42, $p = 0.007$), and disinhibition (p-tau181: OR 2.39, 95% CI 1.45–3.93, $p = 0.001$; p-tau217: OR 2.30, 95% CI 1.33–3.98, $p = 0.003$). In linear regression models, p-tau181 and p-tau217, there was a statistically significant association with NPI-Q severity score (p-tau181: β 0.31, 95% CI 0.13–0.48, $p = 0.001$; p-tau217: β 0.24, 95% CI 0.04–0.45, $p = 0.019$). Associations with Aβ42/Aβ40 were marginal and in the wrong direction; that is, there was an association between Aβ42/Aβ40 and nighttime behavior (OR 1.26, 95% CI 1.00–1.59, $p = 0.046$). There were no associations between NfL and NPS. Please refer to Tables 2 and 3 for an overview of results on the associations between plasma-derived biomarkers and neuropsychiatric symptoms.

In analyses stratified by cognitive status (please refer to Supplementary Material for the full set of models), we observed that among cognitively unimpaired participants, the associations between p-tau181 with agitation (OR 1.88, 95% CI 1.02–3.46, $p = 0.043$), appetite change (OR 2.18, 95% CI 1.38–3.44, $p = 0.001$), disinhibition (OR 2.08, 95% CI 1.03–4.21, $p = 0.041$), and NPI-Q severity score (β 0.27, 95% CI 0.09–0.46, $p = 0.004$), and between p-tau217 and appetite change (OR 1.86, 95% CI 1.08–3.20, $p = 0.025$), as well as between t-tau and appetite change (OR 1.42, 95% CI 1.03–1.95, $p = 0.030$) remained statistically significant. However, the associations between Aβ42/Aβ40 and nighttime behavior, p-tau217 and agitation, p-tau217 and disinhibition, and p-tau217 and NPI-Q severity score no longer remained statistically significant. In contrast, two new statistically significant associations that were not present in the overall sample were observed, that is, between Aβ42/Aβ40 and disinhibition (OR 0.51, 95% CI 0.26–0.99, $p = 0.046$) and between t-tau and agitation (OR 0.46, 95% CI 0.25–0.84, $p = 0.012$), albeit the latter in the wrong direction. Furthermore, in persons with MCI/dementia, we observed a significant association between Aβ42/Aβ40 and BAI total score (β 1.48, 95% CI 0.12–2.85, $p = 0.034$) and NPI-Q severity score (β 0.58, 95% CI 0.05–1.11, $p = 0.031$), albeit in the wrong direction, as well as between t-tau and NPI-Q severity score (β 0.63, 95% CI 0.10–1.16, $p = 0.021$).

4 | DISCUSSION

We observed that higher levels of plasma-derived p-tau181 and p-tau217 were associated with limited number of neuropsychiatric symptoms, that is, increased symptoms of appetite change, agitation, and disinhibition as well as NPI-Q severity score in community-dwelling older adults ≥50 years of age. Specifically, a 1 SD increase in p-tau 181 or p-tau217 corresponded to about 2-fold increased risk of agitation and appetite change, and about 2.5-fold increased risk of disinhibition. This is a significant finding, as previous reports[15] in the MCSA showed that p-tau181 and p-tau217 were very good predictors of elevated brain amyloid and entorhinal cortex tau-PET. Of note, appetite change was the only neuropsychiatric symptom that was also associated with increased t-tau. No statistically significant associations were observed between plasma levels of NfL and neuropsychiatric

TABLE 2 Associations between plasma-derived AD biomarkers and neuropsychiatric symptoms.

	Aβ42/Aβ40		p-tau181		p-tau217	
NPS (Outcome)	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***
Agitation	0.89 [0.57, 1.38]	0.593	1.93 [1.20, 3.11]	**0.007**	2.04 [1.21, 3.42]	**0.007**
Anxiety	0.77 [0.55, 1.09]	0.137	1.11 [0.71, 1.73]	0.648	1.25 [0.77, 2.03]	0.375
Apathy/ indifference	0.97 [0.72, 1.32]	0.858	1.41 [0.94, 2.09]	0.093	1.33 [0.84, 2.10]	0.228
Appetite/ eating change	1.19 [0.91, 1.54]	0.198	2.06 [1.41, 3.00]	**<0.001**	1.70 [1.10, 2.61]	**0.016**
Nighttime behavior	1.26 [1.00, 1.59]	**0.046**	1.19 [0.79, 1.81]	0.405	1.01 [0.61, 1.65]	0.985
Depression/dysphoria	1.04 [0.85, 1.29]	0.692	1.24 [0.90, 1.70]	0.190	1.15 [0.79, 1.67]	0.464
Disinhibition	0.79 [0.49, 1.29]	0.351	2.39 [1.45, 3.93]	**0.001**	2.30 [1.33, 3.98]	**0.003**
Irritability/lability	1.00 [0.79, 1.26]	0.990	1.27 [0.87, 1.84]	0.213	1.26 [0.82, 1.94]	0.284
BDI-II ≥13	1.04 [0.82, 1.32]	0.747	0.92 [0.63, 1.33]	0.646	0.90 [0.57, 1.40]	0.628
BAI ≥10	1.02 [0.81, 1.29]	0.847	0.91 [0.62, 1.32]	0.608	0.83 [0.51, 1.36]	0.463
	***β* [95% CI]**	***p***	***β* [95% CI]**	***p***	***β* [95% CI]**	***p***
NPI-Q severity score	0.04 [−0.07, 0.16]	0.432	0.31 [0.13, 0.48]	**0.001**	0.24 [0.04,0.45]	**0.019**
BDI-II total score	0.03 [−0.29, 0.34]	0.877	0.05 [−0.26, 0.35]	0.761	0.08 [−0.22, 0.37]	0.624
BAI total score	0.11 [−0.19, 0.41]	0.479	0.14 [−0.14, 0.43]	0.322	0.11 [−0.18, 0.39]	0.460

Abbreviations: 95% CI, 95% confidence interval; Aβ, amyloid beta; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptom; OR, odds ratio; p-tau, phosphorylated tau; β, regression coefficient.
For all non-reported NPI-Q-assessed NPS (i.e., delusions, euphoria/elation, hallucinations, motor behavior), there were not enough events to be included in the logistic regression models. Significant *p*-values appear bold; $p < 0.05$, indicates statistical significance.

TABLE 3 Associations between plasma-derived neurodegeneration biomarkers and neuropsychiatric symptoms.

	t-tau		NfL	
NPS (Outcome)	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***
Agitation	0.71 [0.46, 1.10]	0.128	0.91 [0.52, 1.61]	0.753
Anxiety	0.87 [0.63, 1.20]	0.404	0.70 [0.41, 1.20]	0.193
Apathy/indifference	0.99 [0.71, 1.36]	0.936	0.88 [0.57, 1.37]	0.580
Appetite/eating change	1.44 [1.08, 1.92]	**0.012**	1.25 [0.98, 1.59]	0.069
Nighttime behavior	1.21 [0.89, 1.64]	0.217	0.75 [0.45, 1.25]	0.270
Depression/dysphoria	1.12 [0.90, 1.39]	0.308	1.13 [0.90, 1.41]	0.284
Disinhibition	1.34 [0.90, 2.00]	0.149	0.94 [0.53, 1.66]	0.822
Irritability/lability	0.84 [0.64, 1.11]	0.225	0.99 [0.70, 1.40]	0.949
BDI-II ≥13	1.18 [0.93, 1.50]	0.183	1.07 [0.83, 1.37]	0.611
BAI ≥10	0.97 [0.75, 1.24]	0.792	0.97 [0.70, 1.32]	0.824
	***β* [95% CI]**	***p***	***β* [95% CI]**	***p***
NPI-Q severity score	0.04 [−0.07, 0.16]	0.443	0.01 [−0.12, 0.14]	0.890
BDI-II total score	0.17 [−0.14, 0.48]	0.278	0.11 [−0.24, 0.46]	0.531
BAI total score	0.23 [−0.07, 0.53]	0.135	0.16 [−0.17, 0.49]	0.343

Abbreviations: 95% CI, 95% confidence interval; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; NfL, neurofilament light; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptom; OR, odds ratio; t-tau, total tau; β, regression coefficient.
For all non-reported NPI-Q-assessed NPS (i.e., delusions, euphoria/elation, hallucinations, motor behavior), there were not enough events to be included in the logistic regression models. Significant *p*-values appear bold; $p < 0.05$, indicates statistical significance.

symptoms. In addition, we found no clear associations between plasma-derived Aβ42/Aβ40 and neuropsychiatric symptoms, and there was only a marginal association between higher Aβ42/Aβ40 and increased nighttime behavior, which was not in line with our hypothesis.

The literature is not consistent either, and only few studies have examined associations between plasma-derived AD biomarkers and neuropsychiatric symptoms.[42] For example, a cross-sectional study in 995 homebound older adults showed that depression was associated

with lower plasma Aβ42 levels.[21] When the investigators removed persons with cardiovascular disease and those using antidepressant medications from the analyses, they observed an additional association between depression and higher plasma Aβ40/Aβ42 (corresponding to lower Aβ42/Aβ40) indicating a higher degree of amyloid burden. Furthermore, the interaction between depression and high plasma Aβ40/Aβ42 (corresponding to lower Aβ42/Aβ40) was associated with greater cognitive impairment.[21] Similarly, in a cross-sectional study among 86 persons with normal cognition and 53 with MCI selected from the ADNI database, lower plasma Aβ42/Aβ40 was associated with higher MBI total score and greater affective dysregulation, but not with impaired drive/motivation or impulse dyscontrol.[23] A longitudinal study from Europe with 5 years of follow-up among 331 community-dwelling older adults showed that higher plasma Aβ42 levels at baseline predicted late-onset of depression as well as AD, but the interaction between plasma Aβ42 and depression was not associated with the risk of progression to AD.[43] In contrast, a longitudinal study in 223 non-demented individuals found that persons with depression and high plasma Aβ40/Aβ42 (corresponding to lower Aβ42/Aβ40) at baseline were at higher risk of developing incident AD after a mean follow-up of 6 years.[44]

Three studies conducted both cross-sectional and longitudinal analyses on the association between neuropsychiatric symptoms and blood-based biomarkers. A study from Austria showed associations between serum NfL and neuropsychiatric symptoms in cross-sectional but not longitudinal analyses among 237 AD patients.[45] In contrast, research from the United States failed to establish cross-sectional associations between plasma levels of Aβ42 or Aβ42/Aβ40 and depression, but low Aβ42/Aβ40 at baseline was associated with an increased risk of developing depression after 9 years of follow-up in *APOE* ε4 carriers but not in non-carriers.[24] Furthermore, a population-based cohort study among 980 older adults revealed conflicting findings—that is, persons with high Aβ40 levels had more clinically relevant depressive symptoms in cross-sectional analyses at baseline, whereas in longitudinal analyses, persons with low levels of Aβ40 and Aβ42 had a higher risk of developing clinically relevant depressive symptoms over a mean follow-up of 11 years.[46]

Our study adds to the body of literature by showing that plasma-derived AD biomarkers, particularly plasma-derived p-tau, which is specific for AD, is associated with a limited number of neuropsychiatric symptoms. At the same time, we failed to confirm previously reported associations between lower Aβ42/Aβ40 and neuropsychiatric symptoms; however, Aβ42/Aβ40 was also not related to neuropsychiatric symptoms in previous cross-sectional studies.[24] Thus more research is needed to examine the association between plasma Aβ42/Aβ40 and neuropsychiatric symptoms. In general, the differences between previous studies on the associations between plasma-derived biomarkers of AD and neurodegeneration with neuropsychiatric symptoms as reported above, and our current findings may be due to differences in methodology such as tools used to assess neuropsychiatric symptoms, differences in study populations, or different assay designs. Most importantly it must be noted that techniques to determine plasma-derived biomarkers were less reliable a few years ago as compared to single molecule techniques used today; thus, particularly older research should be interpreted with caution.

Our study was about plasma-derived AD biomarkers and neuropsychiatric symptoms. However, in order to interpret our limited findings in the context of the bigger picture, we here provide an overview of the investigation of neuropsychiatric symptoms and AD biomarkers (i.e., amyloid and tau species). To this end, we briefly summarized studies on the associations between CSF-derived and neuroimaging AD biomarkers (i.e., amyloid and tau) with neuropsychiatric symptoms.

With regard to CSF-derived biomarkers, longitudinal research showed that tau/Aβ42 was associated with mood disturbance, anxiety, depression, and confusion, and that tau, ptau181, and tau/Aβ42 were associated with neuropsychiatric symptoms.[8] In cross-sectional analyses, anxiety, agitation, and irritability were associated with abnormal CSF Aβ42, and anxiety with abnormal t-tau concentrations[47]; t-tau/Aβ42 was associated with neuropsychiatric symptom severity[48]; lower Aβ42 and higher t-tau and p-tau were associated with anxiety, and lower Aβ42 with apathy[6]; and lower Aβ42, higher t-tau/Aβ42 and p-tau/Aβ42 were associated with clinical depression, clinical anxiety, apathy, and nighttime behavior.[7] However, studies also reported no associations between CSF biomarkers of t-tau, p-tau, or Aβ42 with apathy or hallucinations.[49]

With regard to amyloid-PET imaging, most cross-sectional studies reported associations between higher neuropsychiatric symptoms burden and higher amyloid load,[9–11,50,51] albeit some studies did not confirm this association.[52,53] Longitudinal studies also provided evidence of associations between neuropsychiatric symptoms, amyloid deposition, and cognitive decline,[54–56] and between abnormal amyloid deposition and higher neuropsychiatric symptoms over time.[57–59] With regard to tau-PET imaging, one cross-sectional study revealed significant associations between higher depressive symptoms with greater inferior temporal and entorhinal cortex tau in cognitively unimpaired older adults,[12] whereas another study showed that neuropsychiatric symptoms were associated with tau-PET in the parietal association area, superior frontal, temporal, and medial occipital lobes.[13]

Although the majority of previous research reported associations between CSF-derived and neuroimaging AD biomarker abnormality (i.e., amyloid and tau) with neuropsychiatric symptoms, our findings were rather limited. We only observed associations between p-tau181, p-tau217, and t-tau with appetite change, and between p-tau181 and p-tau217 with agitation, disinhibition, and NPI-Q severity score, whereas Aβ42/Aβ40 and NfL were not associated with neuropsychiatric symptoms. Thus, studies using CSF-derived or neuroimaging AD biomarkers appear to have more consistent findings as compared to plasma-derived biomarkers. One possible reason may be the continued effort to refine the measurement and interpretation of plasma-derived AD biomarkers in order to demonstrate that plasma-derived biomarkers more accurately reflect the pathological changes in the brain parenchyma.

Because chronic kidney disease is associated with increased levels of the plasma-derived AD biomarkers,[16] we conducted a sensitivity analysis and ran the regression models only among participants

without chronic kidney disease (please refer to the Supplementary Material for the full set of models). We observed consistent and similar results with regard to effect size as in the overall sample, that is, there were statistically significant associations between p-tau181 (OR 2.28, 95% CI 1.49–3.50, $p < 0.001$), p-tau217 (OR 1.86, 95% CI 1.17–2.95, $p = 0.009$), and t-tau (OR 1.51, 95% CI 1.11–2.04, $p = 0.008$) with appetite change. In addition, there were associations between p-tau181 with agitation (OR 1.83, 95% CI 1.06–3.16, $p = 0.031$), and disinhibition (OR 2.17, 95% CI 1.23–3.82, $p = 0.007$), as well as between p-tau217 with agitation (OR 1.93, 95% CI 1.09–3.42, $p = 0.025$), and disinhibition (OR 2.01, 95% CI 1.10–3.66, $p = 0.023$). In linear regression models, p-tau181 (β 0.32, 95% CI 0.12–0.52, $p = 0.001$) and p-tau217 (β 0.24, 95% CI 0.02–0.46, $p = 0.030$) were statistically significantly associated with NPI-Q severity score among participants without chronic kidney disease.

The strengths of our study are the large sample of community-dwelling older adults and the rigorous assessment of both self-reported and informant-observed neuropsychiatric symptoms. In addition, as compared to previous studies that focused mainly on the plasma levels of Aβ42 or Aβ42/Aβ40 and on depression, we included various plasma-derived biomarkers of AD and neurodegeneration as presumed predictor variables in our analyses. Furthermore, because previous work in the MCSA showed that chronic kidney disease is associated with increased levels of plasma-derived AD biomarkers,[16] we were able to perform a sensitivity analysis that resulted in consistent findings with regard to effect size as in the overall sample.

The limitations of our study are the cross-sectional design, which does not allow any conclusion about the direction of the association between plasma-derived biomarkers and neuropsychiatric symptoms. In addition, the number of persons with delusions, euphoria/elation, hallucinations, and motor behavior was too low to be included in the logistic regression analyses. Usually at least 10 events are needed for each predictor included in the logistic regression; thus, even for some neuropsychiatric symptoms (e.g., disinhibition) still included in the analyses, the sample size is a limitation that must be noted and may have affected the estimate precision as reflected in rather large confidence intervals. In addition, the Aβ immunoassay used in this study has less discriminative accuracy than certain mass spectrometry–based methods.[37] Also it is worth noting that we did not examine potential mechanisms that may explain our observed findings. However, we can speculate from the literature that AD pathology as assessed by neuroimaging or plasma-derived biomarkers may lead to increased neuropsychiatric symptoms, albeit other pathways may also be possible (e.g., neuropsychiatric symptoms may have a direct deleterious effect on brain pathology).[60,61] Furthermore, we did not adjust our analyses for multiple comparisons, thereby potentially increasing Type I error. One may apply a Bonferroni correction to our analyses, where the new alpha significance level would be 0.004 (i.e., 0.05/13, since we have a total of 13 models per predictor in Tables 2 and 3). When applying this correction, only 4 of the 10 significant p-values on the associations between plasma-derived biomarkers and neuropsychiatric symptoms would remain significant. It must be noted that statistically significant findings may not always be clinically meaningful. No statistically significant associations were observed between plasma Aβ42/Aβ40 and neuropsychiatric symptoms; however, whether findings would be reproducible if using assays with better discriminative accuracy of amyloid pathology will need to be determined. As mentioned in the Methods section, prior research has reported the AUC between 0.65 and 0.71 with the Quanterix plasma Aβ42/40 assay, which we used in this study, for prediction of amyloid positivity in the BioFinder and ADNI cohorts.[37] In addition, NfL is a biomarker of neurodegeneration not specific to AD and shows the lowest association with AD pathology.[62] Furthermore, limitations pertain to our study sample, which is relatively highly educated, wealthy, and less ethnically diverse; ≈99% of our study participants are White. Although it has been shown that data from Olmsted County are generalizable to the population of Minnesota and the upper Midwest,[63] our findings may not apply to the overall U.S. population. More research is needed, preferably utilizing longitudinal study designs, which allow to examination of the pathways linking plasma-derived biomarkers of AD and neurodegeneration with neuropsychiatric symptoms. Our findings should thus be considered as preliminary until confirmed by prospective studies. Finally, the sample of this analysis was smaller than the full MCSA sample (please also refer to the flow chart of study participation in Figure 1), and limited mainly by the availability of plasma data. When comparing participants included in this analysis to excluded MCSA participants ≥ 50 years of age on key demographic characteristics, we found that the sample included for the current analysis had significantly more male participants, more years of education, more cognitively unimpaired participants, and less presence of anxiety, apathy, nighttime behavior, depression, and hallucinations (data not shown).

In conclusion, higher plasma levels of p-tau181 and p-tau217 are associated with increased symptoms of appetite change, agitation, and disinhibition as well as NPI-Q severity score in community-dwelling older adults. These findings support the validity of plasma tau biomarkers for predicting behavioral symptoms that often accompany cognitive impairment, and also underscore the importance of assessing and potentially treating neuropsychiatric symptoms in clinical practice, particularly among older adults with confirmed plasma-derived biomarker abnormality. More research is needed to confirm our observations.

AUTHOR CONTRIBUTIONS

Janina Krell-Roesch: design and conceptualization of the study, interpretation of the data, drafting the manuscript, revising the manuscript. Isabella Zaniletti: analysis and interpretation of the data, revising the manuscript. Jeremy A. Syrjanen: analysis and interpretation of the data, revising the manuscript. Walter K. Kremers: supervision of analysis and interpretation of the data, revising the manuscript. Alicia Algeciras-Schimnich: data collection, revising the manuscript. Jeffrey L. Dage: data collection, revising the manuscript. Argonde C. van Harten: revising the manuscript. Julie A. Fields: data collection, revising the manuscript. David S. Knopman: data collection, study funding, revising the manuscript. Clifford R. Jack Jr: data collection, study funding, revising the manuscript. Ronald C. Petersen: data collection, study funding,

revising the manuscript. Maria Vassilaki: data collection, analysis and interpretation of the data, revising the manuscript. Yonas E. Geda: data collection, analysis and interpretation of the data, study funding, revising the manuscript.

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CONFLICT OF INTEREST STATEMENT

Walter K. Kremers receives research funding from the Department of Defense, the National Institutes of Health (NIH), Astra Zeneca, Biogen, and Roche. Alicia Algeciras-Schimnich serves on advisory boards for Roche Diagnostics and Fujirebio Diagnostics. Jeffrey L. Dage is an inventor on patents or patent applications of Eli Lilly and Company relating to the assays, methods, reagents, and/or compositions of matter related to measurement of p-tau217. Jeffrey L. Dage has served as a consultant for Genotix Biotechnologies Inc, Gates Ventures, Karuna Therapeutics, AlzPath Inc, Cognito Therapeutics, Inc., and received research support from ADx Neurosciences, AlzPath, Roche Diagnostics, and Eli Lilly and Company in the past 2 years. Jeffrey L. Dage has received speaker fees from Eli Lilly and Company. Argonde C. van Harten served as a consultant for Roche Diagnostics. Julie A. Fields receives research funding from the NIH. David S. Knopman serves on a Data Safety Monitoring Board for the Dominantly Inherited Alzheimer Network (DIAN) study and is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California. Clifford R. Jack Jr. serves on an independent data monitoring board for Roche, has served as a speaker for Eisai, and consulted for Biogen, but he receives no personal compensation from any commercial entity. He receives research support from NIH and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. Ronald C. Petersen consults for Roche, Merck, Genentech, and Biogen, and GE Healthcare and receives royalties from Oxford University Press for the publication of Mild Cognitive Impairment. Maria Vassilaki has received in the past research funding from Roche and Biogen; she currently consults for Roche; receives research funding from NIH; and has equity ownership in Abbott Laboratories, Johnson and Johnson, Medtronic, and Amgen. Yonas E. Geda receives funding from the NIH and Roche and served on the Lundbeck Advisory Board. No other disclosures were reported. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants gave their written informed consent to participate in the Mayo Clinic Study of Aging, in accordance with the ethical standards set by the Mayo Clinic and Olmsted Medical Center institutional review boards.

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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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