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RESEARCH ARTICLE

Association between CSF biomarkers of Alzheimer's disease and neuropsychiatric symptoms: Mayo Clinic Study of Aging

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Abstract

Introduction: We examined the association between cerebrospinal fluid (CSF)-derived biomarkers of Alzheimer's disease and neuropsychiatric symptoms (NPS) in older non-demented adults.

Methods: We included 784 persons (699 cognitively unimpaired, 85 with mild cognitive impairment) aged ≥ 50 years who underwent CSF amyloid beta (Aβ42), hyperphosphorylated tau 181 (p-tau), and total tau (t-tau) as well as NPS assessment using Beck Depression and Anxiety Inventories (BDI-II, BAI), and Neuropsychiatric Inventory Questionnaire (NPI-Q).

Results: Lower CSF Aβ42, and higher t-tau/Aβ42 and p-tau/Aβ42 ratios were associated with BDI-II and BAI total scores, clinical depression (BDI-II ≥ 13), and clinical anxiety (BAI ≥ 10), as well as NPI-Q–assessed anxiety, apathy, and nighttime behavior.

Discussion: CSF Aβ42, t-tau/Aβ42, and p-tau/Aβ42 ratios were associated with NPS in community-dwelling individuals free of dementia. If confirmed by a longitudinal cohort study, the findings have clinical relevance of taking into account the NPS status of individuals with abnormal CSF biomarkers.

KEYWORDS
Alzheimer's disease, cerebrospinal fluid biomarkers, CSF amyloid beta 42, CSF phosphorylated tau, CSF total tau, neuropsychiatric symptoms, non-demented

1 | BACKGROUND

Neuropsychiatric symptoms (NPS) are common in individuals with dementia due to Alzheimer's disease (AD),[1,2] and are also prevalent in mild cognitive impairment (MCI).[3,4] However, the association between AD pathophysiology and NPS remains unclear,[5] particularly in older adults free of dementia. For example, it has been hypothesized that NPS could be a non-cognitive manifestation of AD pathology or a consequence of cognitive decline.[6]

A growing body of research has examined the associations between NPS and neuroimaging[7–9] or plasma biomarkers of AD.[10] However, to date, few studies have been published on the association between cerebrospinal fluid (CSF)-derived biomarkers of AD and NPS in MCI patients;[11-14 and a] limited number of studies have examined the association between CSF-derived biomarkers and NPS in samples including cognitively unimpaired (CU) persons and MCI or AD patients.[15–19] In addition, little is known on the association between several CSF biomarkers of AD (i.e., amyloid beta [Aβ]42, total tau [t-tau], hyperphosphorylated tau 181 [p-tau], t-tau/Aβ42 ratio, p-tau/Aβ42 ratio) with various NPS in a large sample of community-dwelling older adults free of dementia.

Therefore, the aim of the present study was to examine the association between CSF biomarkers of AD with different self- and informant-reported NPS (e.g., depression, anxiety, apathy) in non-demented older adults. We hypothesized that higher neuropathological burden as indicated by lower levels of CSF Aβ42, higher levels of t-tau and p-tau 181, and higher t-tau/Aβ42 and p-tau/Aβ42 ratios would be associated with higher neuropsychiatric burden, that is, increased levels of depression or anxiety, and presence of other NPS such as apathy or agitation.

HIGHLIGHTS

- We studied 784 community-dwelling, non-demented older persons.
- Lower cerebrospinal fluid (CSF) amyloid beta (Aβ)42 was associated with neuropsychiatric symptoms.
- Higher total tau/Aβ42 and hyperphosphorylated tau 181/Aβ42 were associated with neuropsychiatric symptoms.
- Clinicians should consider emotional health of adults with abnormal CSF biomarkers.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed published articles on associations between cerebrospinal fluid (CSF)-derived biomarkers of Alzheimer's disease (AD) and neuropsychiatric symptoms (NPS). Few studies are available, and most have used samples of individuals with prevalent mild cognitive impairment (MCI) or dementia. Thus, our aim was to examine the associations between CSF-derived biomarkers of AD and NPS in non-demented persons, that is, cognitively unimpaired persons and individuals with MCI.
2. Interpretation: Lower CSF amyloid beta (Aβ)42, and higher total tau (t-tau)/Aβ42 and hyperphosphorylated tau 181 (p-tau)/Aβ42 ratios were associated with NPS burden, particularly depression, anxiety, apathy, and nighttime behavior in this large sample of 784 community-dwelling individuals free of dementia.
3. Future directions: We plan to conduct a longitudinal cohort study to further explore our cross-sectional observations. If confirmed, the findings have clinical relevance of taking into account the NPS status of non-demented individuals with abnormal CSF biomarkers.

2 | METHODS

2.1 | Design and sample

We conducted a cross-sectional study derived from the population-based Mayo Clinic Study of Aging (MCSA) in Olmsted County, Minnesota, USA. We included community-dwelling non-demented individuals aged ≥ 50 years; that is, they were either CU or had MCI. The final sample included 784 participants who had undergone a neurological evaluation, risk factor ascertainment, and neuropsychological testing, and also had valid data on CSF Aβ42, p-tau, and t-tau as well as self- and informant-reported NPS. The MCSA was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center and the study also followed Health Insurance Portability and Accountability Act (HIPAA) guidelines. Written informed consent was obtained from all participants.

2.2 | Neurocognitive evaluation

All participants underwent an extensive evaluation including a neurological examination performed by a physician, a risk factor ascertainment conducted by a study coordinator, and standardized neuropsychological testing administered by a psychometrist and supervised by a board-certified neuropsychologist. Details on the procedures of the MCSA have previously been published.[20] Briefly, the neuropsychological test battery assessed performance in four cognitive domains: (1) memory (delayed recall trials from Auditory Verbal Learning Test,[21] logical memory, and visual reproduction subtests from Wechsler Memory Scale-Revised[22]); (2) language (Boston Naming Test[23], category fluency[24]); (3) visuospatial skills (picture completion and block design subtests from Wechsler Adult Intelligence Scale-Revised [WAIS-R][25]); and (4) attention/executive function (Trail-Making Test Part B,[26] digit symbol substitution subtest from WAIS-R[25]). An expert consensus panel consisting of physicians, study coordinators, and neuropsychologists reviewed the results for each participant. The panel then determined whether a participant was CU (based on normative data developed in this community as part of Mayo's Older American Normative Studies[27]) or had MCI based on published criteria.[28,29]

2.3 | CSF measurements

We performed fasting lumbar punctures early in the morning in the lateral decubitus position using a 20- or 22-gauge needle (Quincke). Two cubic centimetres of CSF were used to determine routine markers (i.e., glucose level, protein level, cell count). The remainder was divided into 0.5 cm^3 aliquots and stored at −80°C for future analyses avoiding multiple freeze–thaw cycles before the current analyses.[30] CSF Aβ42,

t-tau, and p-tau were analyzed using Elecsys β-Amyloid(1-42) CSF, Elecsys Total-Tau CSF, and Elecsys Phospho-Tau (181P) CSF electrochemiluminescence immunoassays (Roche Diagnostics).[30] Prior to performing the analysis of the samples included in this article a thorough quality control procedure was performed to determine precision and accuracy of these analyses in our laboratory.[30] For the statistical analysis, we also created t-tau/Aβ42 and p-tau/Aβ42 ratios. Values above and below the technical limits of the assays were handled as described previously.[30]

2.4 | Neuropsychiatric assessment

For this study, we used data from the Beck Depression Inventory (BDI-II[31]), Beck Anxiety Inventory (BAI[32]), and Neuropsychiatric Inventory Questionnaire (NPI-Q[33]). The BDI-II is a self-reported tool that measures common depressive symptoms such as feeling guilty or loss of interest over the past 2 weeks. Similarly, the BAI measures self-reported common anxiety symptoms such as nervousness or fear of losing control over the past 1 week. Both inventories are validated and consist of 21 items. The severity of each item is rated on a scale ranging from 0 to 3; thus, the total score ranges from 0 to 63. A higher score indicates a 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 clinical depression) and BAI score ≥ 10 (indicating clinical anxiety) as categorical measures. The NPI-Q was administered by a study coordinator as a structured interview to an informant, usually the spouse. The NPI-Q assesses the presence or absence of 12 emotional behaviors (i.e., depression, anxiety, apathy, agitation, delusion, hallucination, euphoria, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite).

2.5 | Statistical analysis

Descriptive statistics were calculated and differences in median values or frequencies of variables were compared using Wilcoxon rank sum, Chi-square, or Fisher's exact tests depending on whether the variable was continuous or categorical. As the direction of causality is unknown in cross-sectional studies, we arbitrarily assigned CSF biomarkers as numeric predictors, and considered NPS the outcome of interest of this study. CSF-derived variables (i.e., Aβ42, p-tau, t-tau, t-tau/Aβ42, p-tau/Aβ42) were log-transformed; continuous BDI and BAI measures had 1 added and were also log-transformed. Log-transformation was done because of right-skewed distributions of these variables; 1 had to be added to continuous BDI-II and BAI measures before log-transformation because a log of 0 is mathematically undefined and many participants have a value of 0 for these variables. We conducted linear regression analyses to examine the association between CSF-derived biomarkers and continuous BDI-II and BAI total scores. In addition, we also ran logistic regression analyses to examine the association between CSF-derived biomarkers with BDI-II score ≥ 13 (indicating clinical depression), BAI score ≥ 10 (indicating clinical anxiety), and presence of various NPS as assessed by the NPI-Q (categorical measures). Due to the expected low prevalence of NPS in our population-based sample, we only focused on 7 of the 12 items of the NPI-Q, namely agitation, anxiety, apathy, appetite change, nighttime behavior, depression, and irritability. For the linear models, we computed β-estimates, 95% confidence intervals (CI), and *P* values. For the logistic models, we computed odds ratios (OR), 95% CI, and *P* values. All models were adjusted for age, sex, education, and apolipoprotein E (*APOE*) ε4 carrier status. The linear models were conducted for the overall sample as well as stratified by CU and MCI. The logistic models on clinical depression and anxiety were conducted for the overall sample and the CU subsample where possible as some of the outcomes did not meet the requirement of 10 people in the smallest category for each predictor included in the model. The logistic models on NPI-Q–derived NPS were only conducted for the overall sample. We have not applied a Bonferroni correction to our analyses. However, all models are presented with *P* values in this article, which allows the reader to apply a correction, if so desired, when interpreting our results. All analyses were done using the conventional two-tailed alpha level of 0.05 and performed with SAS 9.4 (SAS Institute, Inc.) and R (R Foundation for Statistical Computing).

3 | RESULTS

The whole sample included 784 participants with a median (range) age of 72.8 (50.7, 95.3) years. Six hundred ninety-nine participants were CU and 85 had MCI. Four hundred forty-six persons (57%) were males, and 212 (27%) were *APOE* ε4 carriers (Table 1). CSF Aβ42 levels were lower, and CSF levels of t-tau, p-tau, t-tau/Aβ42, and p-tau/Aβ42 were higher in participants with MCI than in CU participants. Participants with MCI had higher BDI-II and BAI total scores than CU persons. The frequency of persons with clinically relevant depression (BDI-II score ≥ 13) and anxiety (BAI score ≥ 10) was also higher in the MCI versus CU subsample (Table 1). Finally, frequencies of NPI-Q–assessed anxiety, apathy, appetite change, nighttime behavior, disinhibition, and motor behavior were higher among MCI than CU persons (Table 1).

3.1 | Associations of CSF biomarkers with BDI-II and BAI total scores

CSF levels of Aβ42 (estimate −0.244; 95% CI [−0.379, −0.109]; $P < .001$), t-tau/Aβ42 (est. 0.242; 95% CI [0.108, 0.376]; $P < .001$), and p-tau/Aβ42 (est. 0.219; 95% CI [0.094, 0.343]; $P = .001$) were associated with BDI-II total scores in the overall sample (Table 2). Thus, interpreting in terms of percentages, which log-transforming the predictor and outcome allows, a 1% decrease in CSF levels of Aβ42 was associated with about a 0.24% increase in BDI-II total score; and a 1% increase in t-tau/Aβ42 and p-tau/Aβ42 ratios was associated with about a 0.24% and 0.22% increase in BDI-II total score, respectively. CSF-derived biomarkers of Aβ42, t-tau/Aβ42, and p-tau/Aβ42 were also associated with BDI-II total scores in the CU and MCI subsample (Table 2).

CSF-derived Aβ42 (est. −0.211; 95% CI [−0.346, −0.075]; $P = .002$), t-tau/Aβ42 (est. 0.199; 95% CI [0.065, 0.333]; $P = .004$), and p-tau/Aβ42

TABLE 1 Participant demographics, CSF biomarkers levels, and frequency of neuropsychiatric symptoms

	Total sample (N = 784)	CU (N = 699)	MCI (N = 85)	*P*
Age, median (range)	72.83 (50.72, 95.27)	72.31 (50.72, 95.27)	77.73 (56.39, 92.47)	<.001[a]
Male sex	446 (56.9)	396 (56.7)	50 (58.8)	.703[b]
Education (yrs), median (range)	14 (0, 20)	14 (8, 20)	13 (0, 20)	.002[a]
APOE ε4	212 (27.0)	182 (26.0)	30 (35.3)	.07[b]
Aβ42 (pg/mL), median (range)	1081.5 (222.4, 4255)	1105 (222.4, 3378)	911 (287.3, 4255)	.004[a]
t-tau (pg/mL), median (range)	216.25 (79, 726.7)	213.7 (79, 726.7)	244.8 (92.5, 620)	.002[a]
p-tau (pg/mL), median (range)	18.55 (7, 80.11)	17.99 (7, 80.11)	21.79 (8.89, 65.04)	<.001[a]
t-tau/Aβ42, median (range)	0.18 (0.09, 1.19)	0.17 (0.09, 1.19)	0.24 (0.10, 1.19)	<.001[a]
p-tau/Aβ42, median (range)	0.015 (0.012, 0.024)	0.015 (0.012, 0.022)	0.019 (0.013, 0.043)	<.001[a]
BDI-II total score, median (range)	3 (0, 51)	3 (0, 43){2}	5 (0, 51)	<.001[a]
BDI depression ≥ 13 points	68 (8.7)	51 (7.3){2}	17 (20.0)	<.001[b]
BAI total score, median (range)	1 (0, 40)	1 (0, 40){1}	2 (0, 40)	<.001[a]
BAI ≥ 10 points	63 (8.0)	45 (6.4){1}	18 (21.2)	<.001[b]
NPI-Q				
Agitation	37 (5.1)	30 (4.6){46}	7 (8.9){6}	.105[c]
Anxiety	41 (5.6)	29 (4.4){46}	12 (15.2){6}	<.001[c]
Apathy/indifference	41 (5.6)	32 (4.9){46}	9 (11.4){6}	.033[c]
Appetite/eating change	30 (4.1)	22 (3.4){46}	8 (10.1){6}	.011[c]
Nighttime behavior	53 (8.3)	39 (6.8){128}	14 (20.3){16}	<.001[b]
Delusions	2 (0.3)	1 (0.2){46}	1 (1.3){6}	.204[c]
Depression/dysphoria	87 (11.9)	76 (11.6){46}	11 (13.9){6}	.553[b]
Disinhibition	13 (1.8)	5 (0.8){46}	8 (10.1){6}	<.001[c]
Euphoria/elation	7 (1.0)	5 (0.8){46}	2 (2.5){6}	.169[c]
Hallucinations	0	0{46}	0{6}	/
Irritability/lability	76 (10.4)	66 (10.1){46}	10 (12.7){6}	.483[b]
Motor behavior	6 (0.8)	3 (0.5){46}	3 (3.8){6}	.019[c]

Notes: N (%) unless otherwise stated. {N} = number of participants with missing information. *P*-values based on: [a]Wilcoxon Rank Sum test; [b]Chi-Square test; [c]Fisher Exact test.

Abbreviations: Aβ42, amyloid beta$_{1\text{-}42}$; *APOE* ε4, apolipoprotein E ε4 homozygote or heterozygote; BAI, Beck Anxiety Inventory (range 0–63); BDI-II, Beck Depression Inventory (range 0–63); CSF, cerebrospinal fluid; CU, cognitively unimpaired persons; MCI, persons with mild cognitive impairment; NPI-Q; Neuropsychiatric Inventory Questionnaire; p-tau, phosphorylated tau; t-tau, total tau.

(est. 0.184; 95% CI [0.059, 0.308]; *P* = .004) were associated with total BAI score in the overall sample. In addition, CSF-Aβ42 was associated with BAI total score in the MCI subsample (est. −0.583; 95% CI [−0.998, −0.168]; *P* = .006; Table 2).

3.2 | Associations of CSF biomarkers with categorical BDI-II and BAI

In the total sample, CSF Aβ42 (OR 0.508; 95% CI [0.289, 0.887]; *P* = .018), t-tau/Aβ42 (OR 2.090; 95% CI [1.212, 3.579]; *P* = .007), and p-tau/Aβ42 (OR 1.895; 95% CI [1.138, 3.125]; *P* = .013) were associated with clinical depression (BDI ≥ 13). Similarly, Aβ42 (OR 0.526; 95% CI [0.297, 0.925]; *P* = .026), t-tau/Aβ42 (OR 2.069; 95% CI [1.207, 3.527]; *P* = .008), and p-tau/Aβ42 (OR 1.969; 95% CI [1.193, 3.227]; *P* = .007) were associated with clinical anxiety (BAI ≥ 10; Table 3). In the CU subsample, only t-tau/Aβ42 was associated with clinical depression, and p-tau/Aβ42 was associated with clinical anxiety (Table 3).

3.3 | Associations of CSF biomarkers with NPS as assessed by NPI-Q

CSF Aβ42 (OR 0.293; 95% CI [0.144, 0.586]; *P* = .001), t-tau/Aβ42 (OR 3.366; 95% CI [1.798, 6.338]; *P* < .001), and p-tau/Aβ42 (OR 2.909; 95% CI [1.629,5.208]; *P* < .001) were associated with NPI-Q–assessed presence of anxiety in the total sample (Table 4). Furthermore, CSF Aβ42 was associated with apathy and nighttime behavior, p-tau was associated with nighttime behavior, t-tau/Aβ42 was associated with apathy

TABLE 2 Association of CSF biomarkers with depressive (BDI-II score) and anxiety symptoms (BAI score) in participants without dementia in the MCSA

	CU		MCI		Total sample	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
BDI-II total score						
Aβ42	−0.188 (−0.333, −0.042)	**.011**	−0.501 (−0-.877, -0.125)	**.010**	−0.244 (−0.379, −0.109)	**<.001**
t-tau	−0.024 (−0.214, 0.166)	.805	−0.033 (−0.585, 0.520)	.907	0.006 (−0.174, 0.185)	.952
p-tau	−0.007 (−0.188, 0.175)	.944	−0.051 (−0.554, 0.453)	.841	0.022 (−0.148, 0.192)	.801
t-tau/Aβ42	0.175 (0.029, 0.321)	**.019**	0.433 (0.075, 0.792)	**.018**	0.242 (0.108, 0.376)	**<.001**
p-tau/Aβ42	0.159 (0.024, 0.295)	**.021**	0.373 (0.034, 0.713)	**.032**	0.219 (0.094, 0.343)	**.001**
BAI total score						
Aβ42	−0.129 (−0.271, 0.013)	.075	−0.583 (−0.998, −0.168)	**.006**	−0.211 (−0.346, −0.075)	**.002**
t-tau	0.004 (−0.182, 0.189)	.970	−0.416 (−1.022, 0.189)	.175	−0.012 (−0.191, 0.167)	.895
p-tau	0.019 (−0.158, 0.196)	.832	−0.369 (−0.921, 0.183)	.187	0.009 (−0.160, 0.179)	.914
t-tau/Aβ42 ratio	0.132 (−0.011, 0.274)	.070	0.334 (−0.071, 0.738)	.104	0.199 (0.065, 0.333)	**.004**
p-tau/Aβ42 ratio	0.123 (−0.010, 0.255)	.069	0.285 (−0.097, 0.667)	.142	0.184 (0.059, 0.308)	**.004**

Abbreviations: Aβ42, amyloid beta$_{1\text{-}42}$; *APOE* ε4, apolipoprotein E ε4 homozygote or heterozygote; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory; CI, confidence interval; CSF, cerebrospinal fluid; CU, cognitively unimpaired persons; MCI, persons with mild cognitive impairment; MCSA, Mayo Clinic Study of Aging; p-tau, phosphorylated tau; t-tau, total tau.
Notes: Linear regression models were adjusted for age, sex, education, and *APOE* ε4 carrier status. Significant p-values appear bold.

TABLE 3 Association of CSF biomarkers with depressive (BDI-II ≥ 13) and anxiety (BAI ≥ 10) symptoms in participants without dementia in the MCSA

	CU		Total sample	
	OR (95% CI)	*P*	OR (95% CI)	*P*
BDI-II ≥ 13				
Aβ42	0.607 (0.312, 1.181)	.140	0.508 (0.289, 0.887)	**.018**
t-tau	1.318 (0.571, 3.046)	.517	1.123 (0.547, 2.294)	.752
p-tau	1.223 (0.542, 2.732)	.626	1.101 (0.552, 2.174)	.783
t-tau/Aβ42 ratio	2.090 (1.052, 4.077)	**.032**	2.090 (1.212, 3.579)	**.007**
p-tau/Aβ42 ratio	1.839 (0.965, 3.421)	.058	1.895 (1.138, 3.125)	**.013**
BAI ≥ 10				
Aβ42	0.580 (0.290, 1.159)	.122	0.526 (0.297, 0.925)	**.026**
t-tau	1.203 (0.498, 2.897)	.680	1.251 (0.600, 2.600)	.549
p-tau	1.302 (0.557, 3.009)	.539	1.339 (0.666, 2.666)	.408
t-tau/Aβ42	1.974 (0.984, 3.882)	.051	2.069 (1.207, 3.527)	**.008**
p-tau/Aβ42	1.904 (0.998, 3.555)	**.046**	1.969 (1.193, 3.227)	**.007**

Abbreviations: Aβ42, amyloid beta$_{1\text{-}42}$; *APOE* ε4, apolipoprotein E ε4 homozygote or heterozygote; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory; CI, confidence interval; CSF, cerebrospinal fluid; CU, cognitively unimpaired persons; MCSA, Mayo Clinic Study of Aging; OR, odds ratio; p-tau, phosphorylated tau; t-tau, total tau.
Notes: Logistic regression models were adjusted for age, sex, education, and *APOE* ε4 carrier status. Significant p-values appear bold.

and nighttime behavior, and p-tau/Aβ42 was associated with apathy and nighttime behavior (Table 4).

4 | DISCUSSION

In this cross-sectional study among older adults free of dementia, lower levels of CSF Aβ42 were associated with higher scores in self-reported measures of depressive (BDI-II) and anxiety sympoms (BAI). As expected, this association was stronger in individuals with MCI compared to CU persons. In addition, both increased CSF t-tau/Aβ42 and p-tau/Aβ42 were associated with higher BDI-II and BAI scores in the total sample, as well as in both CU and MCI subsamples. Furthermore, the odds of having clinical symptoms of depression (BDI-II ≥ 13) were on average increased by 2-fold for each unit decrease in log trans-

TABLE 4 Association between CSF biomarkers and NPI-Q assessed neuropsychiatric symptoms in participants without dementia in the MCSA

	Aβ42 OR (95% CI)	t-tau OR (95% CI)	p-tau OR (95% CI)	t-tau/Aβ42 OR (95% CI)	p-tau/Aβ42 OR (95% CI)
Total sample					
Agitation	0.716 (0.348, 1.479)	1.102 (0.427, 2.810)	1.106 (0.449, 2.656)	1.456 (0.713, 2.864)	1.395 (0.717, 2.612)
Anxiety	0.293 (0.144, 0.586)***	1.321 (0.547, 3.170)	1.339 (0.581, 3.032)	3.366 (1.798, 6.338)***	2.909 (1.629, 5.208)***
Apathy/indifference	0.485 (0.245, 0.954)*	1.437 (0.593, 3.460)	1.329 (0.576, 3.006)	2.283 (1.223, 4.219)**	2.001 (1.121, 3.528)*
Appetite/eating change	1.009 (0.457, 2.254)	2.712 (0.982, 7.552)	2.104 (0.817, 5.353)	1.677 (0.803, 3.430)	1.465 (0.736, 2.838)
Nighttime behavior	0.460 (0.251, 0.834)*	2.181 (0.990, 4.812)	2.092 (1.015, 4.291)*	2.689 (1.583, 4.594)***	2.384 (1.468, 3.888)***
Depression/dysphoria	0.766 (0.470, 1.248)	1.073 (0.569, 2.016)	1.020 (0.558, 1.848)	1.344 (0.833, 2.140)	1.262 (0.807, 1.945)
Irritability/lability	0.668 (0.400, 1.113)	0.729 (0.368, 1.428)	0.714 (0.372, 1.348)	1.232 (0.747, 1.998)	1.164 (0.730, 1.824)

Abbreviations: Aβ42, amyloid beta$_{1-42}$; *APOE* ε4, apolipoprotein E ε4 homozygote or heterozygote; CI, confidence interval; CSF, cerebrospinal fluid; MCSA, Mayo Clinic Study of Aging; OR, odds ratio; NPI-Q; Neuropsychiatric Inventory Questionnaire; p-tau, phosphorylated tau; t-tau, total tau.
Notes: For all non-reported NPI-Q categories, there were not enough data in the categories. Logistic regression models were adjusted for age, sex, education, and *APOE* ε4 carrier status. * $.01 < P \leq .05$, ** $.001 < P \leq .01$, *** $P \leq .001$.

formed CSF t-tau/Aβ42 and p-tau/Aβ42. Nearly identical associations exist for these CSF biomarkers with clinical anxiety (BAI ≥ 10). We also observed an association between CSF-derived biomarkers and several NPS as assessed by the informant-reported NPI-Q, that is, lower CSF Aβ42, and higher t-tau/Aβ42 and p-tau/Aβ42 were associated with significantly increased odds of presence of anxiety, apathy, and nighttime behavior. Finally, the odds of having altered nighttime behavior more than doubled on average for each unit increase in log-transformed CSF p-tau 181.

With regard to anxiety, our study is partially in line with previous research. For example, one study reported an association between abnormal CSF levels of Aβ42 or t-tau with more frequent anxiety in persons with MCI.[12] Similarly, investigators from the Netherlands also reported an association between lower levels of CSF Aβ42, and higher levels of t-tau and p-tau with anxiety.[19] In line with this, we also observed associations between higher t-tau/Aβ42 ratio and p-tau/Aβ42 ratio with anxiety (assessed by both self-reported BAI and informant-observed NPI-Q).

Furthermore, in our study we only observed significant associations between CSF amyloid and tau with self-reported (BDI-II) but not informant-observed depression (NPI-Q). In the past, few studies have examined associations between CSF amyloid and tau biomarkers and depression.[11,34] For example, a recent study from the Netherlands did not observe an association between depression and CSF levels of Aβ42, t-tau, or p-tau in persons with subjective cognitive impairment, MCI, and AD.[19] In contrast, a study based on Alzheimer's Disease Neuroimaging Initiative (ADNI) data reported lower CSF Aβ42 levels in MCI persons with compared to without chronic depressive symptomatology assessed using the NPI, but did not observe a difference between groups with regard to CSF tau.[35] A recent review including studies of individuals with AD and MCI even concluded that depression may be associated with lower core AD CSF pathology.[36] More research is needed to examine whether self- or informant-reported depression is associated with CSF-derived biomarkers of AD in older adults free of dementia.

Aside from depression or anxiety, fewer studies have assessed the associations between CSF–biomarker concentrations with other NPS. For example, studies have reported associations between CSF Aβ42 with paranoid or delusional ideation and aggression[17] and apathy[19] as well as agitation and irritability.[12] In addition, associations between CSF t-tau/Aβ42 ratio with irritability, sleep disturbances, and eating disturbances[18] have been reported. On the other hand, several studies failed to establish associations between CSF-derived AD biomarkers with apathy and hallucinations,[16] agitation, irritability, and sleep disturbances[19] or sleep problems.[14] Our study contributes to this body of research by providing preliminary evidence that lower CSF Aβ42, and higher t-tau/Aβ42 and p-tau/Aβ42 are associated with increased odds of presence of apathy and altered nighttime behavior in community-dwelling persons free of dementia. Of note, nighttime behavior entails behavioral disturbances that may occur at nighttime such as sleeplessness, sleep walking, nightmares, or bedwetting, and is the third most common NPS in our dataset (8.3% of the total sample). Given the conflicting findings on potential associations between nighttime behavior and CSF biomarkers, more research is needed that also examines potential mechanisms that may underlie this association.

Overall, as outlined above, there are conflicting findings on the associations between CSF biomarkers of amyloid and tau with depression, anxiety, or other NPS. These discrepancies may be attributed to numerous methodological differences such as sampling method, cognitive and/or biomarker status of participants, sample size, severity of NPS, and instruments used to assess NPS. On average, there appears to be evidence of an association between CSF Aβ42 with NPS, but less so for CSF t-tau or p-tau with NPS.

One possible explanation may be that amyloid peptides change rapidly in the brain,[37] fluctuate diurnaly,[38] and precede many AD changes.[39] These characteristics of amyloid peptides are consistent with the observed association between amyloid peptides and NPS. In fact, characteristics of amyloid peptides contrast with the biology of tau, which is less abrupt and linked to neuronal death and cogni-

tive decline.[40] Increased CSF p-tau and t-tau levels are related to AD. P-tau is associated with neurofibrillary tangle formation in the brain parenchyma,[41];= whereas t-tau not only indicates the severity of neurodegeneration in AD but can also be elevated in other neurodegenerative diseases such as Creutzfeldt-Jakob disease or it can transiently be elevated in stroke or brain trauma. Thus, p-tau may be more AD-specific than t-tau.[42] It has been reported that the sensitivity of progression from MCI to AD for CSF t-tau ranges from 51% to 90% and specificity values range from 48% to 88%; for CSF p-tau, sensitivities range between 40% and 100% and specificities between 22% and 86%, whereas for CSF p-tau/Aβ42, sensitivities are between 80% and 96% and specificities between 33% and 95%.[43] Furthermore, investigators reported that CSF t-tau/Aβ42 and p-tau/Aβ42 were highly concordant with amyloid positron emission tomography (PET) brain imaging classification in the Swedish BioFINDER study involving patients with mild cognitive symptoms (overall percent agreement: 90%; area under the curve [AUC]: 94%) as well as the ADNI database involving individuals with significant memory concern, MCI, or AD (overall percent agreement: 90%; AUC: 96%). In addition, both ratios accurately predicted future disease progression of persons with MCI in the ADNI cohort, and the authors also observed a higher negative percent agreement of tau/Aβ42, which may indicate greater diagnostic utility compared to Aβ42 alone.[44] This is also supported by a literature review[45] and several studies. For example, t-tau/Aβ42 increased concordance with Pittsburgh compound B (PiB) PET standardized uptake value ratio from 85.2% for CSF Aβ42 to 92.5%;[46] and CSF p-tau/Aβ42 in CU individuals showed greater sensitivity for detection of PiB positivity compared to Aβ42 alone.[47] The authors also posit that reasons as to why tau/Aβ42 may be superior over the absolute value of Aβ42 alone, for example, a combination of measures of two different pathologic processes into a single diagnostic biomarker may be more promising, or tau/Aβ42 may reduce random error or variance in Aβ42 measurements.[44]

Overall, more research is needed to untangle the association between CSF-derived biomarkers of amyloid and tau with NPS in presymptomatic AD, and to also investigate mechanisms that may underlie a potential association. Future research should also examine potential associations between CSF neurofilament light chain and neurogranin with NPS.

Of note, our current study confirms observations on the associations between increased BDI and BAI scores and elevated cortical amyloid deposition as measured by PiB-PET that we previously reported based on analyses among CU participants from the same population.[48]

The strengths of our study are the large sample of community-dwelling older adults free of dementia, the detailed assessment of NPS using both self-reported BDI-II and BAI as well as informant-observed NPI-Q, and the large number of CSF-derived biomarkers (i.e., CSF Aβ42, t-tau, p-tau, t-tau/Aβ42, and p-tau/Aβ42). In addition, the study may also be directly relevant to the newly established construct of mild behavioral impairment (MBI), which is considered a neurobehavioral syndrome and refers to the emergence of impactful NPS in late life.[49] MBI represents an at-risk state for new onset of dementia in persons with MCI and is also associated with AD biomarker abnormalities.[50] Furthermore, in line with our observations, a recent study by investigators from Sweden found that CSF p-tau levels were associated with higher scores on the MBI-checklist (MBI-C) in amyloid-positive CU persons. The investigators also report that the MBI-C domains affective regulation and impulse dyscontrol but not drive and motivation, social inappropriateness, or perception and thought were associated with CSF p-tau.[51]

Our study has the following limitations: (1) The cross-sectional study design does not allow for making any conclusions about causality. (2) We did not account for psychotropic medications, and future studies may want to adjust for medication intake. (3) We did not run the analysis stratified for CSF amyloid status (high vs. low CSF Aβ42). It is possible that among participants with elevated t- or p-tau, there may be many individuals without underlying AD pathology (i.e., having high CSF Aβ42) and a potentially existing association between NPS and tau only in participants with AD may be obliterated. (4) We did not additionally control our analyses for global cognitive function because we stratified the analyses by CU and MCI subsamples. However, because we observed that the association between lower levels of CSF Aβ42 with higher BDI-II and BAI was stronger in individuals with MCI compared to CU persons, future prospective cohort studies may need to control for cognition. This would further clarify whether the observed association between CSF biomarkers and depression and anxiety in the overall sample is simply a reflection of the underlying association between cognitive performance and biomarkers. Thus, a potential explanation of our current finding may be that there is no direct association between biomarkers and NPS, but that individuals with cognitive symptoms are more likely to present with depressive or anxiety symptoms and may also have more abnormal biomarkers. (5) Another limitation is that our analyses on the association between CSF biomarkers and NPI-Q–assessed NPS were not stratified by cognitive status (CU and MCI). This was not possible as the number of participants with each NPS is a limiting factor for the logistic models by stratification. Depression and irritability are the only NPS in our dataset for which a stratification may be considered. When we applied stratification, we observed no difference between the results for the overall sample and the CU subset (data not shown). (6) We did not adjust our analyses for multiple comparisons, which may increase Type I error. However, when considering a Bonferroni correction for our analyses, the alpha significance level would be 0.01 (i.e., 0.05/5 because we have a total of five models per predictor and subsample in Tables 2 and 3) and 0.007 (i.e., 0.05/7 since we have a total of seven models per outcome in Table 4). Thus, when taking Table 2 as an example, 8 out of the 13 significant *P* values for the association between NPS and CSF biomarkers would remain significant and none of our major conclusions would be affected by the correction.

In conclusion, this cross-sectional study among non-demented community-dwelling older adults suggests an association between CSF biomarkers of Aβ42, t-tau/Aβ42, and p-tau/Aβ42 with depression, anxiety, apathy, and nighttime behavior. More research, particularly using longitudinal study designs, is needed to confirm this preliminary observation.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

JKR: design and conceptualization of the study, interpretation of the data, drafting the manuscript, revising the manuscript. MR: design and conceptualization of the study, interpretation of the data, drafting the manuscript, revising the manuscript. JAS: analysis and interpretation of the data, revising the manuscript. AvH: revising the manuscript. VL: data collection, study funding, revising the manuscript. CRJ: data collection, study funding, revising the manuscript. WKK: analysis and interpretation of the data, revising the manuscript. DSK: data collection, study funding, revising the manuscript. GBS: study funding, revising the manuscript. RCP: data collection, study funding, revising the manuscript. MV: data collection, analysis and interpretation of the data, revising the manuscript. YEG: data collection, analysis and interpretation of the data, study funding, revising the manuscript.

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