Original Article

Neurobiological correlation between phosphorylated tau and mood symptoms in memory clinic patients

Running title: Association between p-tau and NPS

Takashi Ozaki, MD[1], Naoki Hashimoto MD, PhD[1], Niki Udo, MD, PhD[1], Hisashi Narita, MD, PhD[1], Shin Nakagawa, MD, PhD[2] and Ichiro Kusumi, MD, PhD[1]

[1]Department of Psychiatry, Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

[2]Division of Neuropsychiatry, Department of Neuroscience, Yamaguchi University, Graduate School of Medicine, Ube, Japan

Corresponding author: Naoki Hashimoto MD, PhD

Department of Psychiatry, Graduate School of Medicine, Hokkaido University, Kita 15, Nishi 7, Kita-ku, Sapporo, Japan.

Fax: +81-11-706-5081; Tel: +81-11-706-5160; Email:
hashinao@med.hokudai.ac.jp; orcid.org/0000-0001-8311-7148.

Field of the journal:

BPSD and Intervention, Neuropsychology and Symptomatology

Data availability statement

These data are not publicly available because they contain information that could compromise the privacy of the research participants.

Funding statement

The authors report no financial or other relationship that is relevant to the subject of this article. IK has received honoraria from Boehringer Ingelheim, Eisai, Eli Lilly, Janssen Pharmaceutical, Meiji Seika Pharma, Mochida Pharmaceutical, Novartis Pharma, Otsuka Pharmaceutical, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical, Tsumura, Viatris, and Yoshitomiyakuhin, and has received research/grant support from Asahi Kasei Pharma, Astellas, Daiichi Sankyo, Eisai, Eli Lilly, Mochida Pharmaceutical, Nihon Medi-Physics, Otsuka

Pharmaceutical, Pfizer, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical and Tanabe Mitsubishi Pharma. SN has received honoraria from Sumitomo Pharma, Eisai, Eli Lilly, Lundbeck, Meiji Seika Pharma, MSD, Mylan, Otsuka Pharmaceutical, Pfizer, Shionogi, Takeda Pharmaceutical, Tanabe Mitsubishi Pharma, Tsumura, Jansen Pharmaceutical, Kyowa Pharmaceutical, Kracie and Yoshitomiyakuhin, and has received research/grant support from Sumitomo Pharma, Eisai, Eli Lilly, Mochida Pharmaceutical, MSD, Novartis Pharma, Otsuka Pharmaceutical, Pfizer, Shionogi, Nihon Medi-Physics, Astellas, Tsumura, and Takeda Pharmaceutical. NU has received honoraria from Eisai, MSD, Nihon Medi-Physics, Novartis Pharma, Sumitomo Pharma and Viatris. NH has received personal fees from Janssen Pharmaceutical, Yoshitomiyakuhin, Otsuka Pharmaceutical, Sumitomo Pharma, Takeda Pharmaceutical, and Meiji Seika Pharma. HN and TO have no potential conflicts of interest.

Conflict of interest disclosure

The funding sources had no role in the design, practice or analysis of this study.

55 **Ethics approval statement**

56 The study protocol was approved by the Hokkaido University Institutional

57 Review Board.

58

59 **Patients consent statement**

60 Written informed consent was obtained from each patient or their family before

61 enrolment in the study.

62

63 **Permission to reproduce material from other sources**

64 None

65

66 **Clinical trial registration**

67 Not available

68

Abstract

Background: Alzheimer's disease (AD) dementia and mild cognitive impairment is characterized by impaired cognition accompanied by neuropsychiatric symptoms (NPS) relating to mood, including depression, anxiety, and apathy. However, the utility of AD biomarkers for predicting mood symptoms of NPS remains controversial. Herein, we analysed the relationship between phosphorylated tau (p-tau) and depression, anxiety, and apathy of NPS. We also examined the influence of genetic factors such as apolipoprotein E (APOE) ε4 on these relationships.

Methods: We conducted a cross-sectional survey in older patients (*n*=122) with normal cognition (*n*=12), mild cognitive impairment (*n*=46), and AD (*n*=64) strictly diagnosed by the board of psychiatrists and neurologists of Hokkaido University. NPS of the patients were assessed using the neuropsychiatric inventory questionnaire (NPI). All patients also received a lumbar puncture to obtain cerebral spinal fluid for assessment of p-tau. The inverse probability weighting method was used to adjust for demographic differences between the p-tau present group and the p-tau absent group.

Results: There was an association between p-tau accumulation and decreased

incidence of depression and apathy. APOE ε4 non-carriers also showed a trend towards a negative association between p-tau and depression, which was not evident in APOE ε4 carriers.

Conclusions: We provide new evidence for a negative correlation between p-tau and depression and apathy of NPS, which may be influenced by APOE ε4. Future longitudinal studies are required to confirm the utility of p-tau for predicting the course of mood symptoms in patients with cognitive decline.

Key words: *Alzheimer's disease, mild cognitive impairment, neuropsychiatric symptoms, phosphorylated tau, apolipoprotein E gene*

INTRODUCTION

Alzheimer's disease (AD) dementia is characterized by impaired cognition accompanied by neuropsychiatric symptoms (NPS) related to mood such as depression, anxiety, and apathy.[1–4] These NPS related to mood symptoms (hereafter we refer to as NPS) are prodromal features of AD and mild cognitive impairment (MCI).[5–7] Although early NPS was traditionally associated with frontotemporal dementia, there is growing evidence that NPS (recently termed mild behavioural impairment in MCI patients) may be related to AD progression.[8,9]

Detection of AD biomarkers such as amyloid β 42 (Aβ 42) and phosphorylated tau (p-tau) is important for understanding the development of AD.[10] Many studies suggest that accumulation of AD biomarkers also increases the risk for NPS.[11,12] For example, accumulation of Aβ 42 was associated with increased depression in NPS in elderly patients.[12–16] By contrast, the role of p-tau in NPS remains controversial, with reports of elevated p-tau being either associated with increased risk of NPS[13,17] or having no association.[9,18–23] Interestingly, a few studies have also reported that tau accumulation is associated with a decreased risk of NPS.[19,24,25] The biological processes

116 underlying the relationship between p-tau and NPS remain unclear,[14] although
117 dysregulation of neurotransmitters, the inflammatory system, the serotonergic
118 axis, and neutrophilic factors have been hypothesized.[14,16,19,21,26]

119 NPS may also be modified by genetic factors, such as carriage of the
120 apolipoprotein E epsilon 4 (APOE ε4) allele.[27] Some longitudinal studies have
121 demonstrated that carriage of APOE ε4 is associated with increased risk of NPS
122 in later life.[27] APOE ε4 is a key genetic factor for accelerating cognitive
123 decline,[28] and appears to accelerate cognitive decline together with psychiatric
124 symptoms.[28–30]

125 In the present study, we examined the associations between p-tau,
126 APOE ε4, and NPS in patients admitted to our hospital for a medical checkup
127 related to cognitive impairment. We hypothesized that increasing p-tau
128 concentrations would predict a higher prevalence of NPS, and that APOE ε4
129 would influence this relationship.

130

131 **METHODS**

132 **Participants**

133 Patients were recruited consecutively from referrals to Hokkaido University

Hospital (Sapporo city, Hokkaido, Japan) for a medical checkup of cognitive impairments between 2010 and 2021. Inclusion criteria were age ≥55 years,[9,20,23,24] a new referral for the evaluation of cognitive complaints, and a diagnosis of normal cognition (NC), MCI, or AD in accordance with the diagnostic and statistical manual of mental disorders (4th edition) criteria.[31] Patients who were diagnosed with intellectual disabilities, schizophrenia spectrum disorder, drug abuse, solvent exposure, anoxic brain damage, traumatic head injuries, epilepsy, or other severe physical diseases that may influence cognition were excluded. Patients who fulfilled any of the criteria for dementia with Lewy bodies, frontotemporal dementia, or vascular dementia were also excluded. Trained neurologists participated in all diagnoses, and patients who fulfilled any of the clinical criteria for primary tauopathies such as Pick's disease, progressive supranuclear palsy, or corticobasal degeneration were excluded.[32] Additionally, patients with a Hachinski ischemic score (indicator of vascular damage) ≥4 were excluded.

Cerebrospinal fluid (CSF) was collected from all included patients in the NC (*n*=12), MCI (*n*=46), and AD (*n*=64) groups. A diagnosis regarding dementia and other psychiatric/neurophysiological status was determined by a group of

two or more clinicians with >5 years of clinical experience as a psychiatrist. Other sociodemographic characteristics including age, sex, place of residence, or comorbidities, such as diabetes mellitus, hypertension, any history of cardiovascular disease, or bone fracture, were determined by interview. The activities of daily living were evaluated using the physical self-maintenance scale.[33] The study protocol was approved by the Hokkaido University Institutional Review Board. Written informed consent was obtained from each patient or their family before enrolment in the study.

Clinical assessment

The included patients were assessed using the neuropsychiatric inventory questionnaire (NPI-Q),[34] the mini mental state examination (MMSE),[35] and the clinical dementia rating scale.[36] The NPI-Q is a widely used informant-based measure of NPS that follows up positive screening responses to characterize the severity and caregiver burden in 12 domains of symptoms (the changes in patients are compared with their neuropsychiatric state the month prior). We queried each item with three options: yes, no, or not applicable for medical reasons. The symptoms were evaluated by the patients' careers (i.e., families,

nursing home staff, and nurses). Based on the query findings, we dichotomized NPS as present (1; yes) or absent (0; no and not applicable). NPS is often grouped into three main groups using factor analysis, and one of the three groups is frequently termed ‘mood’ of NPS.[4] Thus, we selected the key neuropsychiatric domains of depression (item 4), anxiety (item 5), and apathy (item 7) for our analysis, all of which belong to ‘mood’ of NPS.[4]

Patients were interviewed on whether they experienced any early onset of depression (EoD) and any antidepressant drug treatment. EoD is defined by the first depressive disorder starting before 60 years of age.[14,37] On the basis of reported criteria,[38] we dichotomized patients with MMSE scores ≥24 as the ‘high MMSE’ group and scores <24 as the ‘low MMSE’ group. Because our included patient population had a mean education length of 11.8 years, we dichotomized patients with an education length ≥12 years as the ‘high educated’ group and those with an education length <12 years as the ‘low educated’ group. In Japan, an education length of 12 years is equivalent to graduating from high school.

Biomarker assessment: CSF collection, storage, and analysis

CSF samples were obtained by lumbar puncture into the L3–L4 or L4–L5

intervertebral spaces with a 23 gauge needle. A total of 12–15 mL of CSF was obtained from each participant in the morning (no fasting required) and placed into polypropylene tubes. Samples were centrifuged at 3,200 g for 10 minutes at 4°C, and the supernatant was divided into 0.5 mL aliquots and stored at −80°C until analysis. The concentration of 181 p-tau in CSF was measured in duplicate by ELISA (Phinoscholar assay; Nipro Parma Corporation, Osaka, Japan) and a plate reader (Infinite F50R; TECAN, Kawasaki, Japan). In brief, following pre-wetting of the filter plate with a wash buffer, a suspension of microspheres containing the corresponding capturing antibodies (AT270) was added to the plate. Next, a mixture of biotinylated detection monoclonal antibodies made for the specific detection of capturing antibodies (HT7) and 100 µL of CSF or standards were added, and the plate was incubated for 60 minutes in the dark. After washing and addition of a detection conjugate (phycoerythrin-labelled streptavidin), the plate was incubated for 30 minutes at room temperature. After further washing and addition of a reading solution (phosphate buffered saline), the assay was analysed on the plate reader. Standard curves were calculated for each biomarker using a sigmoidal curve fitting method, and the mean fluorescence values for duplicate CSF samples were used to establish the

206 concentration of p-tau, as previously reported.[39]

207

208 **CSF outcome measures**

209 Samples were divided into a lower 4th quintile of p-tau concentration group or

210 another group, as previously reported.[17] This resulted in a p-tau cut-off value of

211 >38.2 pg/mL, which is similar to the results of previous studies.[6,40,41] In general,

212 a higher level of p-tau indicates neuronal degeneration.[13]

213

214 **Genetic analysis**

215 To identify the APOE gene, we purified genomic DNA from lymphocytes

216 collected from peripheral blood samples of each patient. For analysis of APOE

217 allele polymorphisms, purified genomic DNA samples were examined as

218 previously described.[42] The APOE protein was measured by a contracted

219 laboratory (LSI Medience Corp., Tokyo, Japan). We dichotomized APOE by the

220 presence or absence of ε4, denoted by the terms ε4 carrier and non-carrier,

221 respectively. An ε4 carrier has the potential to possess one or two ε4 alleles,

222 while a non-carrier has the potential to possess other combinations of APOE,

223 none of which contain ε4.[30]

224

225 **Statistical analysis**

226 The inverse probability weighting method was used to adjust for demographic
227 differences between the p-tau present group and the p-tau absent group.[43] Data
228 from both groups were combined and a logistic regression model with
229 demographic covariates (sex, age, education, diagnosis [i.e., NC, MCI, or AD],
230 EoD, prescription of any antidepressant drugs, and history of major depressive
231 disorders) was used to estimate the propensity score.[44] These covariates are
232 important confounding factors related to the presence or absence of NPI
233 symptoms.[14,18,27,45,46] A standardized propensity score was used to weight the
234 data to keep the total number of included patients constant. When the
235 standardized differences of weighted data between two groups are <0.1, the
236 data are considered appropriately balanced by the propensity score.[47] Using the
237 resulting weighted data, multiple regression models were developed to estimate
238 the odds ratios (ORs) with 95% confidence intervals (95%CI) for the presence
239 of NPI symptoms in relation to the presence of p-tau. Demographic data before
240 and after weighting are shown in Table 2 and Table 3, respectively.

241 To assess genetic influence on the association between NPI symptoms

(depression and apathy) and p-tau, we extracted participants who agreed to provide genetic information (*n*=77). We then divided data into APOE ε4 carrier (*n*=50) and non-carrier (*n*=27) groups. Multiple logistic regression models were used to estimate the ORs with 95%CI for the presence of NPI symptoms in relation to the presence of p-tau for each group. Variables such as sex, age, and diagnosis were considered as potential confounding factors and included in each logistic regression model. Multiple comparison tests with the Bonferroni method were performed, if necessary. To avoid multicollinearity, low correlations between the explanatory variables were included in the multiple logistic regression models by calculating Pearson's correlations between numeric variables, polyserial correlations between numeric and ordinal variables, and polychoric correlations between ordinal variables. Statistical differences were determined at $P < 0.05$. All statistical analyses were performed with statistical software (R version 4.1.1; Foundation for Statistical Computing, Vienna, Austria).[48]

RESULTS

Characteristics of the patients

Data were obtained from 122 patients admitted to Hokkaido University Hospital for a medical checkup for cognitive impairment. The mean age of the patients was 74.0 ± 8.9 years (Table 1), with 60.7% women and the majority living at home. There were 52.5% patients diagnosed with AD, 9.8% diagnosed with NC, and 74.6% with the presence of p-tau. The prevalence of NPS was 67.2%, while the prevalence of depression, anxiety, and apathy was 35.2%, 29.5%, and 30.3%, respectively.

Relationship between presence of depression, anxiety, and apathy of NPI and p-tau in patients with AD, MCI, or NC

After using the inverse probability weighting method to adjust for demographic differences including sex, age, education, diagnosis, EoD, prescription of any antidepressant drugs, and history of major depressive disorders, we analysed the relationship between p-tau and depression, anxiety, and apathy (Table 4). There was an association between decreasing risk of depression (adjusted OR = 0.689 [95%CI = 0.584–0.813]) or apathy (adjusted OR = 0.814 [95%CI = 0.690–0.960]) with p-tau, while there was no association between anxiety and p-tau (adjusted OR = 0.923 [95%CI = 0.783–1.088]). In addition, box plots

showing the relationship between p-tau and neuropsychiatric domains of depression (item 4) and apathy (item 5) are provided in supporting information.

Relationship between presence of depression, anxiety, and apathy of NPI and p-tau in patients with AD, MCI, or NC divided by APOE ε4 carriers and non-carriers

After controlling for confounders, p-tau was associated with decreasing risk of depression (adjusted OR = 0.154 [95%CI = 0.030–0.800]; *P* = 0.026). However, after Bonferroni correction, this was not significant (the *P*-value cut-off for Bonferroni correction is 0.05/2 outcomes = 0.025) in patients without APOE ε4 (Table 5). There was no such association in patients with APOE ε4. We also found no association between p-tau and apathy in APOE ε4 carriers (adjusted OR = 0.307 [95%CI = 0.021–4.441]) and non-carriers (adjusted OR = 0.255 [95%CI = 0.060–1.095]).

DISCUSSION

This study investigated the association between mood/affective symptoms evaluated by NPI and p-tau obtained from CSF. In contrast to our hypothesis,

296 we found that p-tau was associated with a decreasing risk of depression and
297 apathy. Additionally, this association was only observed in APOE ε4 non-
298 carriers, but not in APOE ε4 carriers.

299 To our knowledge, there are very few comparable reports. Numerous
300 studies have reported an association between higher Aβ burden and increased
301 depressive symptoms in older people.[12–16] However, associations between p-
302 tau and NPS in patients with NC, MCI[12], or more severe stages of AD[45] have
303 not been confirmed.[49] Many studies have also reported no associations
304 between p-tau and NPS.[9,18–23] For example, a recent study of patients with
305 asymptomatic cognitive decline from two Canadian cohorts (*n*=115 and *n*=117,
306 respectively) found no association between tau and NPS (depression, anxiety,
307 stress, and apathy) over their longitudinal course, although there was a positive
308 association between tau deposition and NPS at baseline.[23] Similarly, no
309 associations between depression and p-tau were found in AD or cognitively
310 intact patients (*n*=183).[22] Positive associations between p-tau and NPS have
311 also been reported.[13,17] For example, NC patients with elevated tau assessed
312 by positron emission tomography (mean age, 69.5 years) were more likely to be
313 depressed.[13] Furthermore, higher levels of plasma total tau were associated

with elevated NPS such as depression, apathy, and anxiety.[17]

A number of studies have reported associations of p-tau accumulation with decreases in NPS,[19,24,25] which partly supports our findings that p-tau was associated with decreased risk of depression. For example, a memory clinic study that included patients with various types of dementia found a negative correlation between NPI total score and total tau levels.[25] Another hospital-based memory clinic study from Europe also reported a negative correlation between p-tau and the geriatric depression scale, although no adjustment of confounding factors was performed.[19] Interestingly, in patients with a history of seeking medical care, the presence of AD biomarkers was found to be associated with absence of depression.[50] Furthermore, in a longitudinal study using trajectory modelling to explain the different patterns of NPS,[24] two of the five trajectories in depression predicted a decreasing probability of depression in approximately 17% of patients.[24] Similarly, in that study, one of the four trajectories in apathy predicted a decreasing probability of apathy in approximately 10% of patients.[24] Finally, higher p-tau concentrations at baseline were associated with a steep decrease in the probability of apathy.[24]

Given these contrasting findings, the relationship between p-tau and

NPS remains controversial. In general, those studies were limited by small sample sizes, and very few considered the pharmacological treatment status as a confounding factor.[45] Additionally, previous studies have methodological problems involving the laboratory techniques, conditions of CSF sampling, and reagent batches used.[45] Finally, these contrasting findings may be related to the diverse time course of psychiatric symptoms in older people, with some having trajectories with 'increasing' symptoms, but others having trajectories that 'decrease' or have 'no change'.[24,27,46] In our analysis, we considered confounding factors such as sex, age, education, diagnosis of dementia, EoD, prescription of any antidepressant drugs, and history of major depressive disorders, and measured CSF samples in as strict conditions as possible.

In the present study, we found that the negative association between p-tau and depression was only present in APOE ε4 non-carriers, but not in APOE ε4 carriers (although the sample size was small). This suggests that APOE ε4 may exert a modifiable effect on the association between p-tau and depression. APOE was suggested to be an independent risk factor for a chronic increase in NPS.[27] Experimentally, APOE ε4 was also found to accelerate cognitive decline by slowing down the clearance rate of AD pathology.[51] Additionally, APOE ε4

can affect both NPS and cognitive decline.[28,30] For example, APOE ε4 together with NPS including depression, anxiety, and apathy was found to accelerate cognitive decline in MCI patients.[28] Similarly, in a previous study using data from the National Alzheimer's Coordinating Center, the hazard of developing AD in NC patients was 6–12 times higher for APOE ε4 carriers with NPS including depression, anxiety, and apathy.[29] Given these reports, our data suggest that the association between p-tau accumulation and decreased depression can be reduced by APOE ε4. Thus, APOE ε4 may modify the association between NPS and p-tau accumulation.[27,30] However, further longitudinal and biological studies are required to establish a causal relationship.

This study has several limitations. First, the cross-sectional design means that causal relationships could not be determined. Second, because the patients were strictly diagnosed by well-trained psychiatrists and neurologists, our sample size was small. Thus, it may be difficult to detect small effect sizes, with an increased chance of type II errors. Nevertheless, similar sample sizes for evaluating associations between p-tau and depression were previously reported.[1,6,19] In addition, we used the propensity score and adjusted for several confounding factors in the analysis although the sample size was small.

Propensity score methods were originally developed with large sample sizes. However, a recent study showed that among the propensity score methods, inverse probability weighting method can yield appropriate estimations in small sample sizes (40–60) because the method preserves the sample size all along the analysis process and maximizes the available amount of information given.[52] Third, the data were extracted from a single centre. However, referrals were received from various medical institutions, which should increase the generalizability of our study. Fourth, because patients in this study were diagnosed as NC, MCI, or AD, this heterogeneity may make our results difficult to interpret. Nevertheless, similar heterogenous samples have been reported.[24] Fifth, generally, the measurement conditions and techniques used for CSF sampling are heterogenous and considered ambiguous. However, we collected CSF samples in as strict conditions as possible—all patients were admitted to the psychiatric ward of our hospital, and the lumbar punctures were generally performed by the same well-trained neurologist at the same time, on the same day, and in the same bedroom. Finally, because of our limited dataset of Aβ in CSF samples, we could not assess the association between NPS and Aβ.

In conclusion, this study investigated the association between mood

symptoms evaluated using the NPI and p-tau obtained from CSF samples. We found that p-tau was associated with decreasing risk of depression and apathy, and that this association was reduced by APOE ε4. Future longitudinal studies are required to confirm our findings and assess the predictive value of p-tau over the course of mood symptoms in patients with cognitive decline.

ACKNOWLEDGEMENTS

We thank all participants in this study, the psychiatrists and neurologists who discussed their findings with us, and Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

DISCLOSURE STATEMENT

The authors have no potential conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

These data are not publicly available because they contain information that could compromise the privacy of the research participants.

REFERENCES

1. Chan CK, Soldan A, Pettigrew C, et al. Depressive symptoms and CSF Alzheimer's disease biomarkers in relation to clinical symptom onset of mild cognitive impairment. *Alzheimers Dement (Amst).* 2020;**12**:e12106.
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol.* 1999; **56**:303–308.
3. Johnson DK, Watts AS, Chapin BA, Anderson R, Burns JM. Neuropsychiatric profiles in dementia. *Alzheimer Dis Assoc Disord.* 2011;**25**:326–332.
4. Liew TM. Symptom Clusters of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Their Comparative Risks of Dementia: A Cohort Study of 8530 Older Persons. *Journal of the American Medical Directors Association.* 2019; **20**: 1054.e1-1054.e9.
5. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry.* 2016; **24**:823–842.
6. Loureiro JC, Stella F, Pais MV, et al. Cognitive impairment in remitted late-life depression is not associated with Alzheimer's disease-related CSF

biomarkers. *Journal of Affective Disorders.* 2020; **272**:409–416.

7. van Dalen JW, Van Wanrooij LL, Moll van Charante EP, Richard E, van Gool WA. Apathy is associated with incident dementia in community-dwelling older people. *Neurology.* 2018; **90**: e82–89.

8. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *J Alzheimers Dis.* 2017; **56**:929–938.

9. Lussier FZ, Pascoal TA, Chamoun M, et al. Mild behavioral impairment is associated with β‐amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. *Alzheimer's & Dementia.* 2020; **16**:192–199.

10. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018; **14**:535–562.

11. Dafsari FS, Jessen F. Depression—an underrecognized target for prevention of dementia in Alzheimer's disease. *Transl Psychiatry.* 2020; **10**:160.

12. Ng KP, Chiew H, Rosa-Neto P, Kandiah N, Ismail Z, Gauthier S. Associations of AT(N) biomarkers with neuropsychiatric symptoms in

preclinical Alzheimer's disease and cognitively unimpaired individuals. *Transl Neurodegener.* 2021; **10**:11.

13. Babulal GM, Roe CM, Stout SH, et al. Depression is Associated with Tau and Not Amyloid Positron Emission Tomography in Cognitively Normal Adults. *JAD.* 2020; **74**:1045–1055.

14. Dias NS, Barbosa IG, Kuang W, Teixeira AL. Depressive disorders in the elderly and dementia: An update. *Dement neuropsychol.* 2020; **14**:1–6.

15. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry.* 2013; **202**:329–335.

16. Nascimento KKF do, Silva KP, Malloy-Diniz LF, Butters MA, Diniz BS. Plasma and cerebrospinal fluid amyloid-β levels in late-life depression: A systematic review and meta-analysis. *J Psychiatr Res.* 2015; **69**:35–41.

17. Hall JR, Petersen M, Johnson L, O'Bryant SE. Plasma Total Tau and Neurobehavioral Symptoms of Cognitive Decline in Cognitively Normal Older Adults. *Front Psychol.* 2021; **12**:774049.

18. Arnold SE, Xie SX, Leung YY, et al. Plasma biomarkers of depressive

458 symptoms in older adults. *Transl Psychiatry.* 2012; **2**: e65–e65.
459 19. Auning E, Selnes P, Grambaite R, et al. Neurobiological correlates of
460 depressive symptoms in people with subjective and mild cognitive
461 impairment. *Acta Psychiatr Scand.* 2015; **131**:139–147.
462 20. Donovan NJ, Wadsworth LP, Lorius N, et al. Regional cortical thinning
463 predicts worsening apathy and hallucinations across the Alzheimer disease
464 spectrum. *Am J Geriatr Psychiatry.* 2014; **22**:1168–1179.
465 21. Engelborghs S, Maertens K, Vloeberghs E, et al. Neuropsychological and
466 behavioural correlates of CSF biomarkers in dementia. *Neurochem Int.* 2006;
467 **48**:286–295.
468 22. Kramberger MG, Jelic V, Kåreholt I, et al. Cerebrospinal Fluid Alzheimer
469 Markers in Depressed Elderly Subjects with and without Alzheimer's Disease.
470 *Dement Geriatr Cogn Disord Extra.* 2012; **2**:48–56.
471 23. Pichet Binette A, Vachon-Presseau É, Morris J, Bateman R, et al. Amyloid
472 and Tau Pathology Associations With Personality Traits, Neuropsychiatric
473 Symptoms, and Cognitive Lifestyle in the Preclinical Phases of Sporadic and
474 Autosomal Dominant Alzheimer's Disease. *Biol Psychiatry.* 2021; **89**:776–
475 785.

476 24. Banning LCP, Ramakers IHGB, Rosenberg PB, Lyketsos CG, Leoutsakos
477 JMS, Alzheimer's Disease Neuroimaging Initiative. Alzheimer's disease
478 biomarkers as predictors of trajectories of depression and apathy in
479 cognitively normal individuals, mild cognitive impairment, and Alzheimer's
480 disease dementia. *Int J Geriatr Psychiatry.* 2021; **36**:224–234.
481 25. Cotta Ramusino M, Perini G, Vaghi G, et al. Correlation of Frontal Atrophy
482 and CSF Tau Levels With Neuropsychiatric Symptoms in Patients With
483 Cognitive Impairment: A Memory Clinic Experience. *Frontiers in Aging*
484 *Neuroscience*. 2021;**13**. Available from:
485 https://www.frontiersin.org/articles/10.3389/fnagi.2021.595758
486 26. Ledo JH, Azevedo EP, Clarke JR, et al. Amyloid-β oligomers link
487 depressive-like behavior and cognitive deficits in mice. *Mol Psychiatry.* 2013;
488 **18**:1053–1054.
489 27. Holmes SE, Esterlis I, Mazure CM, et al. Trajectories of depressive and
490 anxiety symptoms in older adults: A 6-year prospective cohort study. *Int J*
491 *Geriatr Psychiatry.* 2018; **33**:405–413.
492 28. Valero S, Marquié M, De Rojas I, et al. Interaction of neuropsychiatric
493 symptoms with APOE ε4 and conversion to dementia in MCI patients in a

494 Memory Clinic. *Sci Rep.* 2020; **10**:20058.

495 29. Burke SL, Maramaldi P, Cadet T, Kukull W. Neuropsychiatric symptoms and
496 Apolipoprotein E: Associations with eventual Alzheimer's disease
497 development. *Arch Gerontol Geriatr.* 2016; **65**:231–238.

498 30. Burke SL, Maramaldi P, Cadet T, Kukull W. Associations between
499 depression, sleep disturbance, and apolipoprotein E in the development of
500 Alzheimer's disease: dementia. *Int Psychogeriatr.* 2016; **28**:1409–1424.

501 31. American Psychiatric Association. Diagnostic and Statistical Manual of
502 Mental Disorders, 4th edn, text revision edn. American Psychiatric
503 Association, Washington, DC, 2000.

504 32. Zhang Y, Wu KM, Yang L, Dong Q, Yu JT. Tauopathies: new perspectives
505 and challenges. *Mol Neurodegeneration.* 2022; **17**:28.

506 33. Lawton MP, Brody EM. Assessment of Older People: Self-Maintaining and
507 Instrumental Activities of Daily Living1. *The Gerontologist.* 1969; **9**:179–186.

508 34. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA,
509 Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of
510 psychopathology in dementia. *Neurology.* 1994; **44**:2308–23014.

511 35. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical

512 method for grading the cognitive state of patients for the clinician. *J Psychiatr*
513 *Res.* 1975; **12**:189–198.
514 36. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and
515 staging measure for dementia of the Alzheimer type. *Int Psychogeriatr.* 1997;
516 **9** Suppl 1:173–176; discussion 177-178.
517 37. Diniz BS, Teixeira AL, Machado-Vieira R, et al. Reduced Cerebrospinal Fluid
518 Levels of Brain-Derived Neurotrophic Factor Is Associated With Cognitive
519 Impairment in Late-Life Major Depression. *The Journals of Gerontology*
520 *Series B: Psychological Sciences and Social Sciences.* 2014; **69**:845–851.
521 38. Kim J, Schweizer TA, Fischer CE, Munoz DG. Psychosis In “Cognitively
522 Asymptomatic” Elderly Subjects Is Associated with Neuritic Plaque Load, Not
523 Neurofibrillary Tangles. *Alzheimer Dis Assoc Disord.* 2018; **32**:185–189.
524 39. Hoshi K, Kanno M, Abe M, et al. High Correlation among Brain-Derived
525 Major Protein Levels in Cerebrospinal Fluid: Implication for Amyloid-Beta and
526 Tau Protein Changes in Alzheimer’s Disease. *Metabolites.* 2022; **12**:355.
527 40. Forlenza OV, Diniz BS, Teixeira AL, et al. Effect of brain-derived
528 neurotrophic factor Val66Met polymorphism and serum levels on the
529 progression of mild cognitive impairment. *The World Journal of Biological*

Psychiatry. 2010; **11**:774–780.

41. Guo T, Korman D, La Joie R, et al. Normalization of CSF pTau measurement by Aβ40 improves its performance as a biomarker of Alzheimer's disease. *Alz Res Therapy.* 2020; **12**:97.

42. Ikeda M, Okamoto K, Suzuki K, et al. Recurrent Lobar Hemorrhages and Multiple Cortical Superficial Siderosis in a Patient of Alzheimer's Disease With Homozygous APOE ε2 Allele Presenting Hypobetalipoproteinemia and Pathological Findings of 18F-THK5351 Positron Emission Tomography: A Case Report. *Front Neurol.* 2021; **12**:645625.

43. Rubin DB. The use of propensity scores in applied Bayesian inference. In: Bayesian Statistics 2. North-Holland/Elsevier, Amsterdam; New York, 1985; 463-472.

44. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983; **7**: 41-55.

45. Banning LCP, Ramakers IHGB, Deckers K, Verhey FRJ, Aalten P. Affective symptoms and AT(N) biomarkers in mild cognitive impairment and Alzheimer's disease: A systematic literature review. *Neurosci Biobehav Rev.* 2019; **107**:346–359.

548 46. Mirza SS, Wolters FJ, Swanson SA, et al. 10-year trajectories of depressive
549 symptoms and risk of dementia: a population-based study. *Lancet Psychiatry.*
550 2016; **3**:628–635.
551 47. Austin PC. Using the Standardized Difference to Compare the Prevalence of
552 a Binary Variable Between Two Groups in Observational Research.
553 *Communications in Statistics - Simulation and Computation.* 2009; **38**:1228–
554 1234.
555 48. R Core Team. R: A Language and Environment for Statistical Computing
556 [Internet]. Vienna, Austria; 2016. Available from: https://www.R-project.org/
557 49. Cummings J. The Neuropsychiatric Inventory: Development and
558 Applications. *J Geriatr Psychiatry Neurol.* 2020; **33**:73–84.
559 50. Espenes R, Kirsebom BE, Eriksson C, et al. Amyloid Plaques and
560 Symptoms of Depression Links to Medical Help-Seeking due to Subjective
561 Cognitive Decline. *JAD.* 2020; **75**:879–890.
562 51. Jiang Q, Lee CYD, Mandrekar S, et al. ApoE Promotes the Proteolytic
563 Degradation of Aβ. *Neuron.* 2008; **58**:681–693.
564 52. Pirracchio R, Resche-Rigon M, Chevret S. Evaluation of the propensity
565 score methods for estimating marginal odds ratios in case of small sample size.

566 *BMC Med Res Methodol* 2012; **12**: 70.

567

568 **Table 1** Characteristics of the patients (*n*=122)

Variables		
Total, *n*	122	
Women, *n* (%)	74	(60.7)
Age, mean (SD) (years)	74	(8.9)
PSMS, mean (SD)	7.7	(4.0)
Education, mean (SD) (years)	11.8	(3.1)
High educated, *n* (%)	75	(61.5)
Low educated, *n* (%)	47	(38.5)
Current place of residence, *n* (%)		
Home	115	(94.3)
Institute of care facilities	7	(55.7)
Comorbidities, *n* (%)		
Diabetes mellitus	20	(16.4)
Cardiovascular diseases	13	(10.7)
Hypertension	10	(8.2)
Bone fracture	51	(41.8)
Diagnosis for underlying cause of dementia, *n* (%)		

NC	12	(9.8)
MCI	46	(37.7)
AD	64	(52.5)
MMSE, mean (SD)	23.1	(4.7)
High MMSE, *n* (%)	67	(54.9)
Low MMSE, *n* (%)	55	(45.1)
CDR, *n* (%)		
0	11	(9.0)
0.5	43	(35.2)
1	50	(41.0)
2	14	(11.5)
3	4	(3.3)
Early age of depression, *n* (%)	9	(7.4)
Use of antidepressants, *n* (%)	14	(11.5)
p-tau, mean (SD)	57.0	(30.9)
p-tau (+), *n* (%)	91	(74.6)
p-tau (−), *n* (%)	31	(25.4)
NPI-Q, *n* (%)		

Any of the symptoms	82	(67.2)
Depression (item-4)	43	(35.2)
Anxiety (item-5)	36	(29.5)
Apathy (item-7)	37	(30.3)

569 Abbreviations: SD, standard deviation; PSMS, physical self-maintenance scale;
570 HIS, Hachinski ischemic score; MMSE, mini mental state examination; CDR,
571 clinical dementia rating scale; EoD, early onset of depression; NC, normal
572 cognition; MCI, mild cognitive impairment; AD, Alzheimer's disease; NPI-Q,
573 neuropsychiatric inventory questionnaire.

574

Table 2 Characteristics of patients with p-tau and without p-tau in Alzheimer's disease, mild cognitive impairment, and normal cognition groups before propensity score matching

Characteristics	p-tau (−)		p-tau (+)		Absolute standardized differences, %
Female, *n* (%)	17	(54.8)	57	(62.6)	0.078
Age, mean (SD)	72.0	(9.1)	74.8	(8.8)	0.306
High education, *n* (%)	20	(64.5)	55	(60.4)	0.041
Early diagnosis of depression, *n* (%)	4	(12.9)	5	(5.5)	0.074
MMSE ≥24, *n* (%)	22	(71.0)	45	(49.5)	0.215
NC, *n* (%)	10	(32.3)	2	(2.2)	0.014
MCI, *n* (%)	12	(38.7)	34	(37.4)	0.014
AD, *n* (%)	9	(29.0)	55	(60.4)	0.314
Use of antidepressant drugs, *n* (%)	3	(9.7)	11	(12.1)	0.024

Abbreviations: EoD, early onset of depression; MMSE, mini mental state

579 examination; NC, normal cognition; MCI, mild cognitive impairment; AD,

580 Alzheimer’s disease; NPI-Q, neuropsychiatric inventory questionnaire.

581

582 **Table 3** Characteristics of patients with p-tau and without p-tau in Alzheimer's
583 disease, mild cognitive impairment, and normal cognition groups after
584 propensity score matching

Characteristics	p-tau (−)		p-tau (+)		Absolute standardized differences, %
Female, *n* (%)	13	(66.9)	47	(62.20)	0.046
Age, mean (SD)	74.9	(8.8)	74.1	(8.90)	0.099
High education, *n* (%)	13	(66.9)	49	(64.60)	0.023
Early diagnosis of depression, *n* (%)	2	(8.5)	8	(10.10)	0.017
MMSE ≥24, *n* (%)	10	(50.7)	41	(53.80)	0.032
NC, *n* (%)	2	(9.2)	6	(7.50)	0.017
MCI, *n* (%)	6	(34.2)	29	(38.50)	0.043
AD, *n* (%)	11	(56.6)	41	(54.00)	0.026
Use of antidepressant drugs, *n* (%)	4	(19.0)	9	(11.70)	0.073

585 Abbreviations: EoD, early onset of depression; MMSE, mini mental state

586 examination; NC, normal cognition; MCI, mild cognitive impairment; AD,

587 Alzheimer’s disease; NPI-Q, neuropsychiatric inventory questionnaire.

588

589 **Table 4** Relationship between the presence of depression, anxiety, and apathy of neuropsychiatric inventory questionnaire

590 (NPI-Q) and p-tau in patients with Alzheimer's disease, mild cognitive impairment, or normal cognition

NPI-Q		p-tau (+)			
		n	AOR	95%CI	*P*-value
Depression (item-4)	Present	43	0.689	0.584–0.813	$P < 0.001^{\dagger}$
	Absent	79	Reference		
Anxiety (item-5)	Present	36	0.923	0.783–1.088	0.339
	Absent	86	Reference		
Apathy (item-7)	Present	37	0.814	0.690–0.960	$0.016^{\dagger}$
	Absent	85	Reference		

591 Abbreviations: AOR, adjusted odds ratio; 95%CI, 95% confidence intervals. Note: We used weighted data (inverse

592 probability weighting method) and adjusted for confounding factors including sex, age, education, diagnosis of dementia,

593 early onset of depression, prescription of any antidepressant drugs, and history of major depressive disorders. †Statistically

594 significant after Bonferroni correction ($P < 0.0167$).

595

596 **Table 5** Relationship between the presence of depression, anxiety, and apathy of neuropsychiatric inventory questionnaire

597 (NPI-Q) and p-tau in patients with Alzheimer's disease, mild cognitive impairment, or normal cognition grouped by

598 apolipoprotein E epsilon 4 (APOE ε4) carriers and non-carriers

NPI-Q		p-tau (+) with APOEε4 carrier				p-tau (+) with APOEε4 non-carrier			
		n	AOR	95%CI	*P*-value	*N*	AOR	95%CI	*P*-value
Depression (item-4)	Present	11	0.344	0.042–2.834	0.321	13	0.154	0.030–0.800	0.026†
	Absent	16	Reference			37	Reference		
Apathy (item-7)	Present	9	0.307	0.021–4.441	0.386	15	0.255	0.060–1.095	0.066
	Absent	18	Reference			35	Reference		

599 Abbreviations: AOR, adjusted odds ratio; CI, confidence intervals. Note: The AOR for presence of depression or apathy in

600 relation to p-tau was calculated using a logistic regression model controlling for age, sex, and underlying cause of dementia.

601 †$P < 0.05$ before Bonferroni correction; $P > 0.05$ after Bonferroni correction (the P-value cut-off for Bonferroni correction is

602 0.05/2 outcomes = 0.025).

603

SUPPORTING INFORMATION

Figure S1. Box plots showing the relationship between phosphorylated tau (p-tau) (pg/mL) and neuropsychiatric domains of depression (item 4) (present or absent).

Figure S2. Box plots showing the relationship between phosphorylated tau (p-tau) (pg/mL) and neuropsychiatric domains of apathy (item 5) (present or absent).