# Plasma P-Tau181 and Neuropsychiatric Symptoms in Preclinical and Prodromal Alzheimer Disease

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## ABSTRACT

Objective: Plasma p-tau181, a well-validated marker of Alzheimer's disease (AD) pathological change, could be a more efficient way to diagnose AD than invasive or expensive biomarkers requiring cerebrospinal fluid or positron emission tomography. In some individuals, neuropsychiatric symptoms (NPS) are the earliest manifestation of AD, observed in advance of clear cognitive decline. However, the few studies assessing AD biomarkers in association with NPS have often suffered from imprecision in capturing behavioral symptoms that represent sequalae of neurodegenerative disease. Thus, the mild behavioral impairment (MBI) construct was developed, framing NPS in a way to improve the precision of risk estimates for disease. MBI core criteria stipulate that NPS emerge de novo in later-life and persist for at least six months. Here, cross-sectionally and longitudinally, we investigated associations of MBI with p-tau181, neuropsychological test performance, and incident AD.

Methods: Cognitively unimpaired and mild cognitive impairment (MCI) Alzheimer Disease Neuroimaging Initiative participants were selected. MBI status was derived from the Neuropsychiatric Inventory (NPI) using a published algorithm. NPI total scores at baseline and year-one visits were used to operationalize MBI (score>0 at both visits), NPS not meeting MBI criteria (NPS-not-MBI, score>0 at only one visit), and no-NPS (score=0 at both visits). Linear regressions were fitted for cross-sectional analyses; multilevel linear mixed-effects and Cox proportional hazards models were implemented to examine longitudinal associations of MBI with changes in p-tau181 and cognition, and incident dementia.

Results: The sample included 571 participants (age 72.2, 46.8% female, 64.8% MCI). Cross-sectionally (Beta=8.1%, 95%CI:1.4%-15.2%, p=0.02) MBI was associated with higher plasma ptau-181 levels compared to no-NPS; NPS-not-MBI was not. Longitudinally, MBI was associated with higher p-tau181 (Beta=0.014%, 95%CI:0.003-0.026, p=0.02), in addition to a decline in memory and executive function. Survival analyses demonstrated a 3.92-fold greater dementia incidence in MBI, with no significant differences between NPS-not-MBI and no-NPS.

Discussion: These findings extend the evidence base that MBI is associated with elevated risk of cognitive decline and dementia, and a sequela of emerging Alzheimer-related proteinopathies. MBI offers a substantial improvement over current approaches that explore behavior as a proxy marker for Alzheimer-related proteinopathies, with both clinical and AD trial enrichment implications.

**Table 1. Sample characteristics for the three neuropsychiatric symptoms (NPS) groups: MBI, NPS-not-MBI, and no NPS.** P-values were calculated based on two-sample t-tests for continuous variables and Chi-squared test for categorical variables. Abbreviations: MBI: mild behavioral impairment; MMSE= Mini Mental State Examination; NPS= neuropsychiatric symptoms; Q1= the first quartile; Q3= the third quartile; SD= standard deviation.

| Characteristics | MBI (N=103) | NPS-not-MBI (N=135) | No NPS (N=333) | MBI vs No NPS *p* value | NPS-not-MBI vs No NPS *p* value |
|---|---|---|---|---|---|
| **Age** | | | | | |
| Mean (SD) | 72.1 (7.25) | 72.2 (7.14) | 72.2 (7.03) | 0.85 | 0.96 |
| **Education** | | | | | |
| Median [Q1-Q3] | 16 [14-18] | 16 [14.6-18.4] | 16 [14.5-18.5] | 0.46 | 0.36 |
| **Sex** | | | | | |
| Male | 76 (73.8%) | 69 (51.1%) | 159 (47.7%) | **<0.001** | 0.58 |
| Female | 27 (26.2%) | 66 (48.9%) | 174 (52.3%) | | |
| **MMSE** | | | | | |
| Mean (SD) | 28.4 (1.44) | 28.2 (1.74) | 28.6 (1.54) | 0.16 | **0.03** |
| **Plasma ptau-181**[1] | | | | | |
| Median [Q1-Q3] | 16 [11.8-22.4] | 14.4 [9.8-21.4] | 13.8 [9.5-20.8] | **0.008** | 0.56 |

[1] The plasma ptau-181 values are raw values before log-transformation, but the t-tests were performed on values after log-transformation.

**Table 2. Cross-sectional associations between MBI and plasma p-tau181, compared to NPS-not-MBI and plasma p-tau181.** Plasma p-tau181 values were log-transformed. The reference group for NPS groups, was no NPS. Abbreviations: CI= confidence interval; MBI= mild behavioral impairment; MMSE= Mini Mental State Examination; NPI/NPI-Q= neuropsychiatric inventory/neuropsychiatric inventory questionnaire; NPS= neuropsychiatric symptoms.

| Outcome | Predictor | Beta[1] | 95% CI | *p* value |
|---|---|---|---|---|
| Plasma p-tau181 | MBI vs. no NPS | 8.1% | +1.4% to +15.2% | **0.02** |
| | NPS-not-MBI vs. no NPS | 1.7% | -3.9% to +7.7% | 0.55 |
| | Age | 0.7% | +0.3% to +1.0% | **<0.001** |
| | Education | -0.2% | -1.1% to +0.7% | 0.64 |
| | Sex | 1.7% | -3.0% to +6.7% | 0.48 |
| | MMSE | -1.6% | -3.0% to -0.1% | **0.03** |
| | NPI/NPI-Q [NPIQ-NPI] | -3.5% | -9.2% to +2.5% | 0.24 |
| | NPI/NPI-Q [NPI-Q] | -15.3% | -37.4% to +17.6% | 0.34 |

[1] Beta coefficients represent the estimate percent difference in the plasma ptau-181 biomarker.

**Table 3. Longitudinal association between annual measures of both MBI (between-person NPS changes) and NPS-not-MBI (within-person NPS changes), and plasma p-tau181 over four years using linear mixed effects models.** The model was adjusted for age, sex, education, cognitive diagnosis, source of NPS data, and time. P-tau181 values were log-transformed. Abbreviations: CI= confidence interval; MBI= mild behavioral impairment; MMSE= Mini Mental State Examination; NPI/NPI-Q= neuropsychiatric inventory/neuropsychiatric inventory questionnaire; NPS= neuropsychiatric symptoms.

| Outcome | Predictor | Beta | 95% CI | *p* value |
|---|---|---|---|---|
| Plasma p-tau181 | MBI vs. no NPS | 0.014 | 0.003 to 0.026 | **0.02** |
| | NPS-not-MBI vs. no NPS | 0.0004 | -0.006 to 0.007 | 0.89 |
| | Age | 0.0079 | 0.005 to 0.012 | **<0.001** |
| | Education | -0.0009 | -0.008 to 0.006 | 0.80 |
| | Sex | 0.0175 | -0.021 to 0.056 | 0.37 |
| | MMSE | -0.0074 | -0.013 to -0.002 | **0.004** |
| | NPI/NPI-Q [NPI-NPIQ] | -0.0126 | -0.06 to -0.035 | 0.60 |
| | NPI/NPI-Q [NPIQ] | -0.186 | -0.433 to 0.06 | 0.14 |
| | Years | 0.0096 | 0.004 to 0.016 | **0.002** |

[1] Beta coefficients represent the estimate percent difference in the plasma ptau-181 biomarker.

**Table 4. Longitudinal association between annual measures of MBI (between-person NPS changes) and NPS-not-MBI (within-person NPS changes), and changes in cognitive task performance over four years using linear mixed effects models.** All models were adjusted for age, sex, education, cognitive diagnosis, source of NPS data, and time. The reference group for MBI and NPS-not-MBI, was no NPS. Abbreviations: CI= confidence interval; MBI= mild behavioral impairment; NPS= neuropsychiatric symptoms; RAVLT= Rey Auditory Verbal Learning Test.

| Outcome | Predictor | Beta | 95% CI | *p* value |
|---|---|---|---|---|
| **RAVLT immediate change** | MBI | -0.40 | -0.64 – -0.16 | **0.001** |
| | NPS-not-MBI | -0.12 | -0.31 – 0.07 | 0.229 |
| **RAVLT learning change** | MBI | -0.13 | -0.20 – -0.07 | **<0.001** |
| | NPS-not-MBI | -0.02 | -0.09 – 0.05 | 0.521 |
| **RAVLT %forgetting change** | MBI | 1.21 | 0.36 – 2.05 | **0.005** |
| | NPS-not-MBI | -0.18 | -0.94 – 0.58 | 0.635 |
| **Trail-making B change** | MBI | 1.31 | 0.02 – 2.60 | **0.046** |
| | NPS-not-MBI | 0.37 | -0.77 – 1.50 | 0.526 |

**Figure 1. Flowchart illustrating the step-by-step process of inclusion/exclusion criteria of the present study.** ADNI= Alzheimer's Disease Neuroimaging Initiative; CU= cognitively unimpaired; MBI= mild behavioral impairment; MCI= mild cognitive impairment; NPI= neuropsychiatric inventory; NPI-Q= neuropsychiatric inventory questionnaire; NPS= neuropsychiatric symptoms.

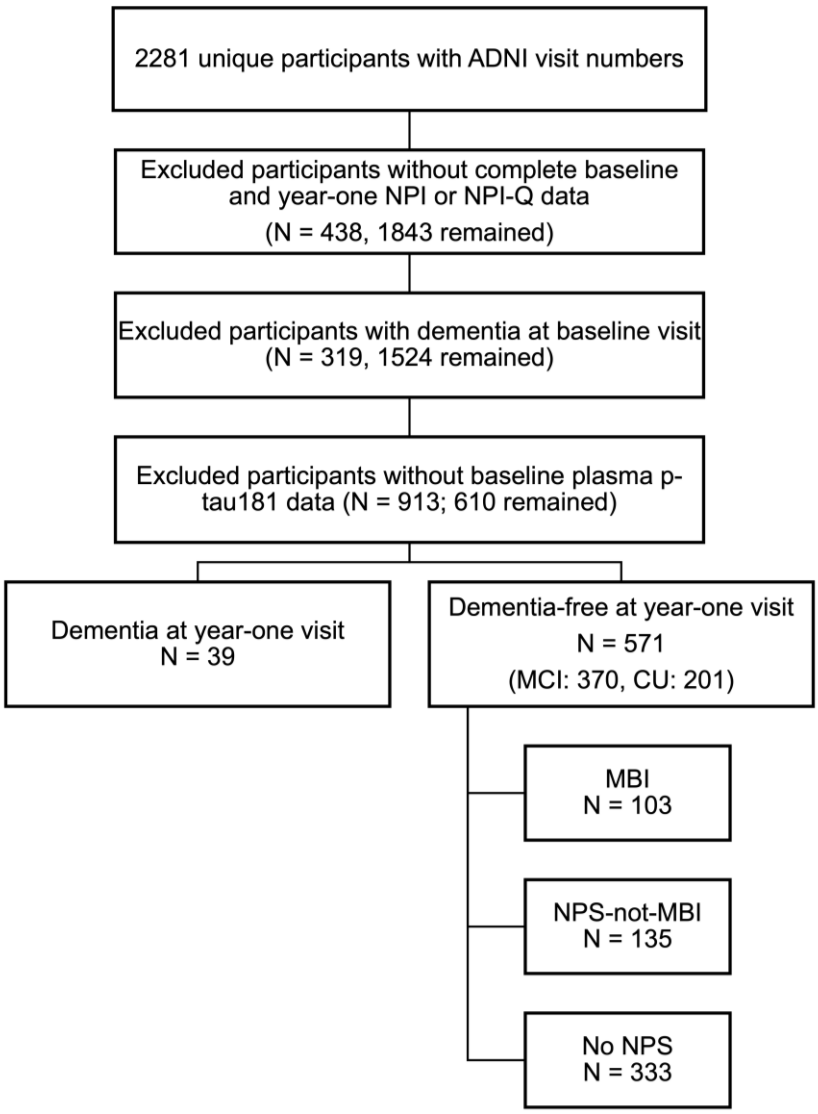



**Figure 2. Violin plot of the distribution of unadjusted log-transformed plasma ptau-181 values at baseline across neuropsychiatric symptoms (NPS) categories.** In each NPS category, grey dots represent individual datapoints of log-transformed ptau-181 values and the embedded box plot in blue represents the median, 25$^{th}$, and 75$^{th}$ percentiles. MBI= mild behavioral impairment; NPS= neuropsychiatric symptoms.

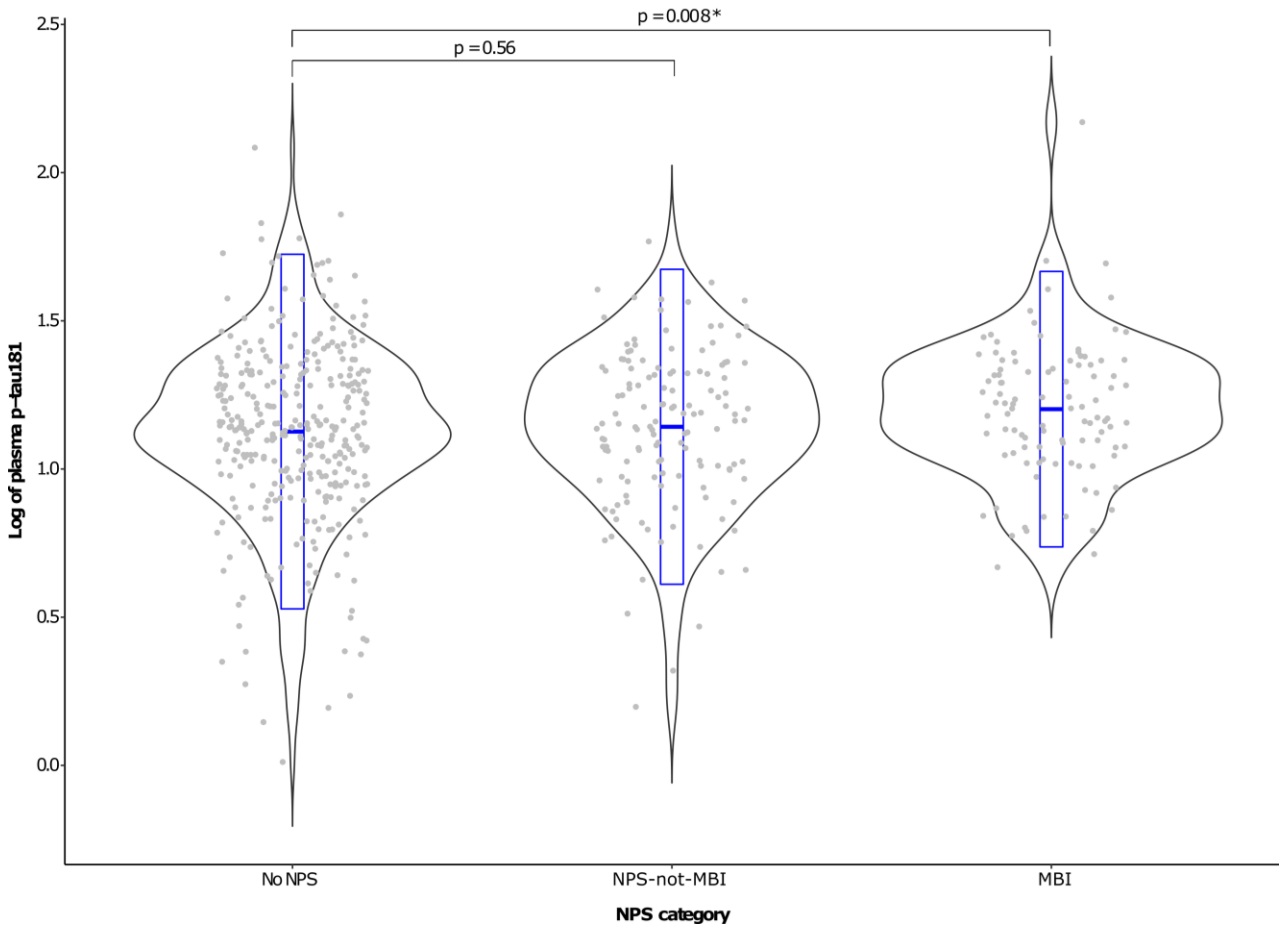
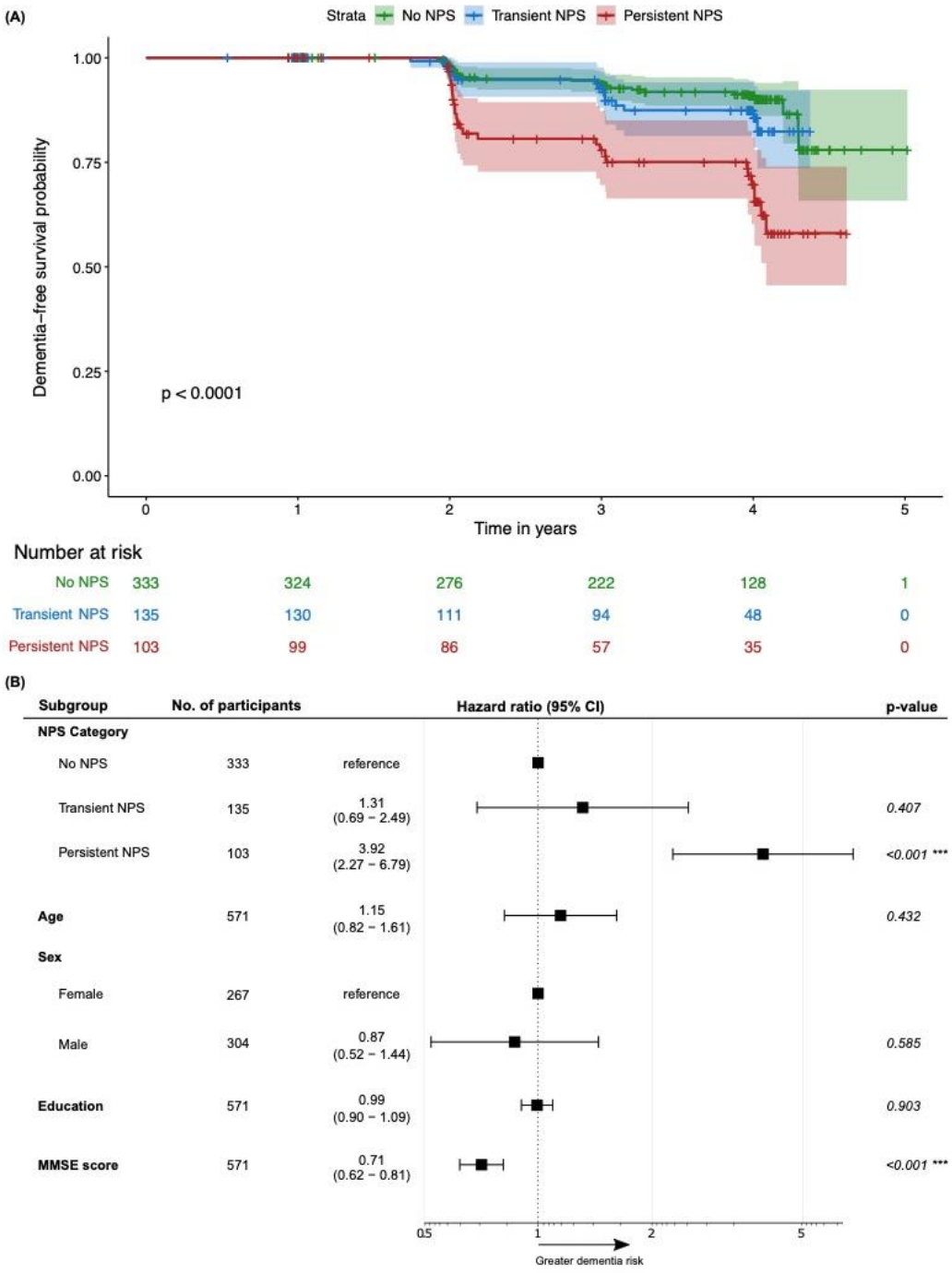



**Figure 3. Kaplan Meier survival curves and adjusted hazard ratios for dementia across neuropsychiatric symptoms (NPS) categories. (A)** Dementia-free survival curves across NPS categories: no NPS, NPS-not-MBI, and MBI. **(B)** Forest plot of adjusted hazard ratios for dementia across NPS categories. Error bars represent the 95% confidence intervals. CI= confidence interval; MBI= mild behavioral impairment; MMSE= Mini Mental State Examination; NPS= neuropsychiatric symptoms.


(A)
Strata No NPS Transient NPS Persistent NPS
1.00
0.75
0.50
0.25
0.00
Dementia−free survival probability
p < 0.0001
0
1
2
3
4
5
Time in years
Number at risk
No NPS 333 324 276 222 128 1
Transient NPS 135 130 111 94 48 0
Persistent NPS 103 99 86 57 35 0
(B)
Subgroup
No. of participants
Hazard ratio (95% CI)
p-value
NPS Category
No NPS 333 reference
Transient NPS 135 1.31 (0.69 − 2.49) 0.407
Persistent NPS 103 3.92 (2.27 − 6.79) <0.001 ***
Age 571 1.15 (0.82 − 1.61) 0.432
Sex
Female 267 reference
Male 304 0.87 (0.52 − 1.44) 0.585
Education 571 0.99 (0.90 − 1.09) 0.903
MMSE score 571 0.71 (0.62 − 0.81) <0.001 ***
0.5
1
2
5
Greater dementia risk