RESEARCH ARTICLE

Optimizing detection of Alzheimer's disease in mild cognitive impairment: a 4-year biomarker study of mild behavioral impairment in ADNI and MEMENTO

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Abstract

Background Disease-modifying drug use necessitates better Alzheimer disease (AD) detection. Mild cognitive impairment (MCI) leverages cognitive decline to identify the risk group; similarly, mild behavioral impairment (MBI) leverages behavioral change. Adding MBI to MCI improves dementia prognostication over conventional approaches of incorporating neuropsychiatric symptoms (NPS). Here, to determine if adding MBI would better identify AD, we interrogated associations between MBI in MCI, and cerebrospinal fluid biomarkers [β-amyloid (Aβ), phosphorylated-tau (p-tau), and total-tau (tau)-ATN], cross-sectionally and longitudinally.

Methods Data were from two independent referral-based cohorts, ADNI (mean[SD] follow-up 3.14[1.07] years) and MEMENTO (4.25[1.40] years), collected 2003–2021. Exposure was based on three-group stratification: 1) NPS meeting MBI criteria; 2) conventionally measured NPS (NPSnotMBI); and 3) noNPS. Cohorts were analyzed separately for: 1) cross-sectional associations between NPS status and ATN biomarkers (linear regressions); 2) 4-year longitudinal repeated-measures associations of MBI and NPSnotMBI with ATN biomarkers (hierarchical linear mixed-effects models-LMEs); and 3) rates of incident dementia (Cox proportional hazards regressions).

Results Of 510 MCI participants, 352 were from ADNI (43.5% females; mean [SD] age, 71.68 [7.40] years), and 158 from MEMENTO (46.2% females; 68.98 [8.18] years). In ADNI, MBI was associated with lower Aβ42 (standardized β [95%CI], -5.52% [-10.48-(-0.29)%]; $p = 0.039$), and Aβ42/40 ($p = 0.01$); higher p-tau (9.67% [3.96–15.70%]; $p = 0.001$), t-tau (7.71% [2.70–12.97%]; $p = 0.002$), p-tau/Aβ42 ($p < 0.001$), and t-tau/Aβ42 ($p = 0.001$). NPSnotMBI was associated only with lower Aβ42/40 ($p = 0.045$). LMEs revealed a similar 4-year AD-specific biomarker profile for MBI, with NPSnotMBI associated only with higher t-tau. MBI had a greater rate of incident dementia (HR [95%CI], 3.50 [1.99–6.17; $p < 0.001$). NPSnotMBI did not differ from noNPS (HR 0.96 [0.49–1.89]; $p = 0.916$). In MEMENTO, MBI demonstrated a similar magnitude and direction of effect for all biomarkers, but with a greater reduction in Aβ40. HR for incident dementia was 3.93 ($p = 0.004$) in MBI, and 1.83 ($p = 0.266$) in NPSnotMBI. Of MBI progressors to dementia, 81% developed AD dementia.

Conclusions These findings support a biological basis for NPS that meet MBI criteria, the continued inclusion of MBI in NIA-AA ATN clinical staging, and the utility of MBI criteria to improve identification of patients for enrollment in disease-modifying drug trials or for clinical care.

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Background

Inefficiencies and failures in the Alzheimer disease (AD) clinical trial program for disease-modifying therapies (DMTs) have been attributed to suboptimal detection of early phase illness [1]. Imprecise case ascertainment of prodromal AD based on standard clinical assessment requires further investigation. However, detailed neuropsychological testing and imaging, and cerebrospinal fluid (CSF) or positron emission tomography (PET) studies are laborious, expensive, and not universally available [2–7]. High screen-failure rates inflate costs, rendering some trials infeasible. Simple, inexpensive, and scalable proxy markers that improve AD detection in participants with mild cognitive impairment (MCI) are needed to reduce biomarker screen failures and improve trial efficiency. Further, in clinical care, as AD monoclonal antibody DMTs become available for use, finding clinical proxy markers that would help better identify ATN-framework-consistent AD is also an unmet need.

Neuropsychiatric or mental health symptoms (NPS) in older adults can initially emerge early in the disease course; 30% of AD cases present with NPS in advance of a cognitive diagnosis [8]. Mild Behavioral Impairment (MBI) is a syndrome that exploits this early manifestation of NPS to identify a high-risk group for incident cognitive decline and dementia [9, 10]. The ISTAART-AA criteria for MBI stipulate that NPS must emerge de novo in later life and persist for at least 6 months to qualify. This behavioral risk group is also described in the NIA-AA research framework for AD [10, 11]. In NIA-AA Stage 2, i.e., normal cognition or subjective cognitive decline (SCD), the staging description indicates that while cognition is the core feature, mild neurobehavioral symptoms, which have a recent onset and which persist, may coexist and may even be the primary complaint in some. In Stage 3, i.e., MCI, the framework indicates that while cognitive impairment is the core clinical criterion, neurobehavioral disturbance may be prominent in the clinical presentation [10, 11]. This linkage between the NIA-AA biological framework for AD and MBI provides further impetus to explore ATN biomarker correlates of neurobehavioral symptoms.

It is important to emphasize that MBI must be interpreted in the context of cognitive risk. MBI is not a competing construct or alternative to MCI, interpreted absent cognitive status, but is a complementary or add-on marker of risk, modifying the risk estimate for a specific cognitive status (i.e., NC, SCD, or MCI) [11–13].

Using these criteria, studies have demonstrated a significantly higher incidence rate of cognitive decline and dementia across cognitive categories in participants with MBI compared to participants with no NPS or with NPS not meeting MBI criteria (NPSnotMBI) [12–25]. Specific to MCI, recent findings showed that when participants were stratified by NPS status (i.e., noNPS, NPSnotMBI, MBI), MBI had a higher progression rate to dementia, and a lower reversion rate to normal cognition (CN) [13]. These findings demonstrate the utility of behavioral-risk stratification (represented by MBI) in conjunction with cognitive-risk stratification (represented by MCI) to improve specificity, and highlight the advantage of the MBI framework over conventional NPS models. However, biomarker confirmation of AD status in MCI progressors is required to better understand these associations, and to move this approach forward into clinical trial recruitment and clinical care.

Preliminarily, plasma, CSF, and PET data have demonstrated mostly cross-sectional associations between MBI and amyloid and p-tau [26–28]. Definitive studies are still required. Here, our aims were to determine if combining a behavioral assessment (informed by MBI criteria) together with a cognitive assessment (informed by MCI criteria) would identify a subgroup with: 1) greater baseline AD pathology (β-amyloid42, p-tau, t-tau); 2) greater change in AD biomarker levels over 4 years; and 3) greater 4-year incidence rate of dementia, specifically AD. The goal was not to determine if adding MBI to biomarkers would improve the performance of the biomarker models, but rather to determine if pre-screening with MBI could improve AD detection and prognostication via subsequent biomarker analysis, and improve our mechanistic understanding of the behavioral prodrome of AD.

Methods

ADNI and MEMENTO

Primary testing was in the Alzheimer's Disease Neuroimaging Initiative (ADNI), a partnership involving multiple centers across North America with the goal of tracking participants through periods of cognitive decline and dementia. Launched in 2003, ADNI continues to evaluate biomarker, neuroimaging, and neuropsychological status in participants. All data used in this study were obtained prior to December 2021. Only participants with MCI were included in our study, to represent Stage 3 of the NIA-AA framework.

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Validation was in the French MEMENTO cohort study [29], which recruited 2323 memory clinic patients with subjective cognitive complaints between April 2011 and June 2014. Participants were ≥ 60 years old, and MCI was defined as performance 1.5 SD below age and education adjusted norms in ≥ 1 cognitive domain (memory, language, praxis, visuospatial or executive function). Participants underwent clinical and neuropsychological assessments, brain MRI, and were reassessed at 6-month intervals. A subset of MEMENTO participants had CSF biomarker sampling in addition to regular assessments. Similarly, only participants with MCI were included.

Sample

The study flowchart is shown in Fig. 1. Participants were included if they had complete Neuropsychiatric Inventory (NPI) or Neuropsychiatric Inventory Questionnaire (NPI-Q) [30] data for the first (baseline), and second (1-year) visits. A total of 510 MCI participants were included in the analysis, all with CSF measures at baseline. Biomarkers included β-amyloid42 (Aβ42), β-amyloid40 (Aβ40), p-tau, t-tau, and Aβ42/Aβ40, p-tau/Aβ42, and t-tau/Aβ42 ratios.

MBI case ascertainment

NPI or NPI-Q scores were used to determine NPS status. The NPI and NPI-Q consist of 12 NPS domains, scored for frequency and/or severity over a 1-month reference range. NPI/NPI-Q domains were used to derive MBI domains using a published algorithm [31]: MBI motivation/drive (apathy) from apathy/indifference; MBI emotional regulation (mood/anxiety symptoms) from the sum of depression, anxiety, and elation/euphoria; MBI impulse control (agitation, aggression, impulsivity) from the sum of irritability, agitation/aggression, and aberrant motor behavior; MBI social inappropriateness (impaired social cognition) from disinhibition; and MBI abnormal thoughts/perception (psychotic symptoms) from delusions/hallucinations. Converted NPI/NPI-Q scores for these 10 domains were then transformed into the 5 MBI domains; sleep and appetite changes were not included in the algorithm. Baseline and one-year visits were used to operationalize the MBI symptom persistence criterion. For each visit, a transformed NPS total score > 0 was classified as NPS + . Two consecutive NPS + visits were classified as MBI (i.e., persistent NPS); and a conventional NPS + score at one visit was classified as NPSnotMBI (i.e., transient NPS). Two consecutive NPS- visits were classified as noNPS.

Statistical analysis

Basic demographic information was abstracted (age, sex, education, and Mini-Mental State Examination (MMSE) score). NPS groups (MBI, NPSnotMBI) were compared against the noNPS group using Chi-squared tests (categorical variables) and independent *t*-tests (continuous variables).

Linear regressions were fitted to determine cross-sectional associations between NPS status as independent variable, and CSF biomarkers as continuous dependent variables. Logarithmic transformations were applied to CSF biomarker measures due to skewness. All models
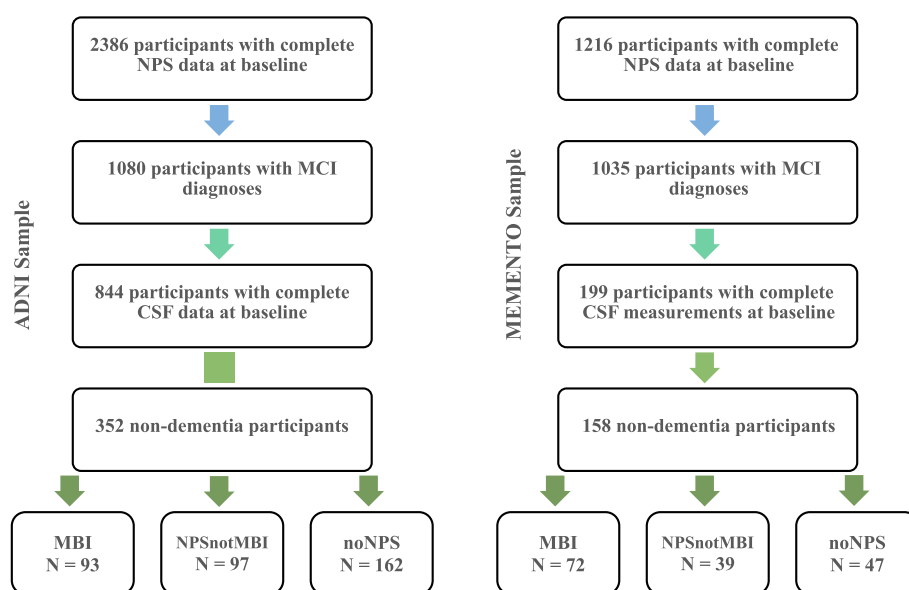

Fig. 1 Flowchart showing how the sample populations were obtained from the ADNI and MEMENTO datasets

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adjusted for age, sex, education, MMSE scores and the source of NPS (NPI or NPI-Q). MBI status was coded using dummy variables, corresponding to MBI, NPSnot-MBI, and noNPS groups. Contrasts were set up for comparisons against the noNPS group. NPS source was coded using dummy variables, corresponding to NPI for both visits, NPI-Q for both visits, or a combination of NPI and NPI-Q; NPI for both visits was the reference.

Hierarchical linear mixed-effects (LME) models were implemented to assess the longitudinal relationship between NPS profile and CSF biomarkers over the span of 4 years. Annual NPS measure was predictor, and concurrent annual measure of CSF biomarker level was outcome. Time-varying covariates were leveraged to capture stable between-person NPS differences (consistent with MBI symptom persistence) and within-person visit-to-visit variability (consistent with impersistent or transient NPS, i.e., NPSnotMBI). Using a person-centered approach, the between-person NPS predictor was calculated as the mean total NPS score across all visits, and the within-person NPS predictor was calculated as the NPS score for each visit minus the between-person NPS score [32]. Participant ID was modeled as a random effect. Fixed effects include age, sex, education, NPS (between- and within-person), MMSE, time, diagnosis, and NPS scale (NPI, NPI-Q, combination).

Kaplan–Meier survival curves were generated to compare dementia-free survival probability for the 3 groups (MBI, NPSnotMBI, noNPS). Cox proportional hazards regressions were utilized to compare rates of progression from MCI to dementia as a function of NPS status (MBI, NPSnotMBI, noNPS), while controlling for age, sex, years of education, and MMSE score at baseline. ADNI did not provide information on dementia subtypes, but MEMENTO did. Thus, dementia progressors in MEMENTO were further reported by percentage of participants in each dementia subtype. For the ADNI dataset, statistical analyses were performed using R (version 4.2.2). For the MEMENTO validation dataset, analyses were performed using R (version 4.1.3) on the Dementias Platform UK Data Portal (DPUK). Assumptions of linear regression were satisfied, assessed using the *ggfortify* package in R. Linearity was assessed with a Martingale residuals plot. Assumptions for Cox proportional hazards were satisfied, tested using a Schoenfeld test and linearity was assessed with a Martingale residuals plot from the *survival* and *survminer* packages in R.

Results
ADNI
The ADNI sample comprised 352 participants (43.5% females; mean [SD] age, 71.68 [7.40] years). NPS group was determined using the NPI in 235 participants, and NPI-Q in 117 participants. Demographic information is shown in Table 1. Linear regressions showed that compared to noNPS, MBI was associated with lower CSF Aβ42

Table 1 Sample characteristics at baseline

	Characteristics	Overall (n=352)	MBI (n=93)	NPSnotMBI (n=97)	noNPS (n=162)	*p*-values [2]	
						MBI	NPSnot MBI
ADNI	Age, mean (SD)	71.68 (7.40)	71.72 (7.37)	72.35 (7.42)	71.25 (7.42)	0.6191	0.247
	Female sex, n (%)	153 (43.5%)	24 (25.8%)	42 (43.3%)	87 (53.7%)	**<0.001**	0.136
	Education [1]	16 (14 − 18)	16 (14 − 18)	16 (14 − 18)	16 (14 − 18)	0.5948	0.494
	MMSE [1]	28 (27 − 29)	28 (27 − 29)	28 (27 − 29)	29 (27 − 29)	0.7399	0.664
	CSF biomarkers [1]						
	Aβ42	914 (693 − 1326)	811 (610 − 1326)	920 (670 − 1239)	935 (757 − 1468)	**0.0493**	**0.054**
	Aβ40	8458 (6548 − 10003)	8657 (6614 − 10247)	7916 (6411 − 9605)	8638 (6545 − 10047)	0.6919	0.672
	p-tau	22.3 (16.4 − 31.5)	24.2 (18.5 − 37.5)	21.8 (15.7 − 30.6)	21.2 (16.0 − 28.4)	**0.0110**	0.795
	t-tau	243 (186 − 321)	271 (207 − 363)	238 (171 − 317)	239 (187 − 303)	**0.0235**	0.922
	Aβ42/Aβ40	0.12 (0.09 − 0.18)	0.10 (0.08 − 0.18)	0.11 (0.08 − 0.16)	0.13 (0.09 − 0.19)	**0.0087**	0.063
	p-tau/Aβ42	0.02 (0.01 − 0.04)	0.03 (0.01 − 0.06)	0.03 (0.01 − 0.04)	0.02 (0.01 − 0.04)	**0.0045**	0.195
	t-tau/Aβ42	0.25 (0.13 − 0.43)	0.33 (0.15 − 0.53)	0.27 (0.13 − 0.45)	0.21 (0.13 − 0.40)	**0.0058**	0.239
	Characteristics	Overall (n=158)	MBI (n=72)	NPSnotMBI (n=39)	noNPS (n=47)	*p*-values [2]	
						MBI	NPSnot MBI
MEMENTO	Age, mean (SD)	68.98 (8.18)	69.12 (7.55)	68.20 (8.55)	69.41 (8.90)	0.8539	0.5242
	Female sex, n (%)	73 (46.2%)	32 (44.4%)	19 (48.7%)	22 (46.8%)	0.9483	1.0000
	MMSE [1]	28 (27 − 29)	28 (27 − 29)	28 (27 − 29)	28 (27 − 29)	0.1368	0.3493
	CSF biomarkers [1]						
	Aβ42	948 (679 − 1311)	879 (615 − 1249)	1163 (696 − 1425)	1073 (730 − 1345)	**0.0339**	0.9519
	Aβ40	13553 (10775 − 16729)	12747 (10530 − 16251)	14266 (10811 − 17011)	13698 (11364 − 17033)	**0.0720**	0.4362
	p-tau	57.2 (43.8 − 74.7)	59.3 (45.1 − 92.2)	56.1 (40.5 − 67.1)	52.8 (41.9 − 67.8)	**0.0184**	0.7211
	t-tau	304 (225 − 513)	331 (235 − 631)	344 (200 − 473)	260 (228 − 426)	**0.0693**	0.5487
	Aβ42/Aβ40	0.08 (0.05 − 0.11)	0.07 (0.05 − 0.11)	0.08 (0.06 − 0.11)	0.09 (0.05 − 0.10)	0.5285	0.6420
	p-tau/Aβ42	0.05 (0.04 − 0.11)	0.07 (0.04 − 0.14)	0.04 (0.03 − 0.08)	0.04 (0.03 − 0.08)	**0.0067**	0.7954
	t-tau/Aβ42	0.29 (0.18 − 0.67)	0.37 (0.19 − 0.95)	0.27 (0.16 − 0.61)	0.25 (0.17 − 0.54)	**0.0219**	0.6422

[1] Median values and interquartile ranges are shown. Cerebrospinal fluid biomarkers values are shown raw. [2] t-tests (two-tailed) were performed on log-transformed values. MBI and NPSnotMBI compared to noNPS. Abbreviations: MBI=Mild Behavioural Impairment; MMSE=Mini-Mental State Exam

level and Aβ42/40 ratio, higher p-tau and t-tau levels, and higher t-tau/Aβ42 and p-tau/Aβ42 ratios; NPSnotMBI was associated only with lower Aβ42/40 (Table 2).

Longitudinal biomarker measures were available in 161/352 participants at two years, 99/352 at three years, and 216/352 at four years. LME models tracking the sample over 4 years showed that higher between-person NPS differences (i.e., MBI) were associated with lower CSFAβ42 level and Aβ42/40 ratio, higher CSF p-tau and t-tau levels, and higher p-tau/Aβ42 and t-tau/Aβ42 ratios. Within-person NPS variability (i.e., NPSnotMBI) only associated with slightly higher t-tau (Table 3).

During follow-up (mean [SD], 3.14 [1.07] years), 70 participants progressed from MCI to dementia. Kaplan–Meier survival curves demonstrated significantly lower dementia-free survival at 4 years in the MBI group relative to NPSnotMBI and noNPS (Fig. 2a). Cox regression showed that individuals with MBI had a 3.5-fold greater incidence rate of dementia while NPSnotMBI did not differ from noNPS (HR = 0.96).

MEMENTO

The MEMENTO sample comprised 158 participants (46.2% females; mean [SD] age, 68.98 [8.18] years). NPS group was determined using NPI alone. Demographic information is shown in Table 1. Linear regressions showed that compared to noNPS, MBI was associated with lower CSF Aβ42 level, higher p-tau, and higher p-tau/Aβ42 and t-tau/Aβ42 ratios; NPSnotMBI did not significantly differ from noNPS on any of the measures (Table 2).

Longitudinal CSF measures were available in 77/158 participants at two years, 47/158 at three years, and 72/158 at four years. LME models showed that MBI was associated with higher CSF p-tau levels, and higher p-tau/Aβ42 and t-tau/Aβ42 ratios; NPSnotMBI was not associated with any of the measures (Table 3).

During follow up (mean [SD], 4.25 [1.40] years), 42 participants progressed from MCI to dementia. Kaplan–Meier survival curves demonstrated significantly lower dementia-free survival at 4 years in the MBI group relative to the NPSnotMBI and noNPS groups (Fig. 2b). The

Table 2 Association between NPS group and CSF biomarkers modeled using linear regression models

	Outcome	Predictor	Standardized β	95% CI		p-value
				Lower	Upper	
ADNI	Aβ42	MBI	-5.52%	-10.48%	-0.29%	**0.039**
		NPSnotMBI	-4.61%	-9.40%	0.44%	0.073
	Aβ40	MBI	2.00%	-1.57%	5.70%	0.275
		NPSnotMBI	-0.26%	-3.60%	3.20%	0.883
	p-tau	MBI	9.67%	3.96%	15.70%	**0.001**
		NPSnotMBI	1.09%	-3.96%	6.40%	0.677
	t-tau	MBI	7.71%	2.70%	12.97%	**0.002**
		NPSnotMBI	0.06%	-4.40%	4.73%	0.979
	Aβ42/40	MBI	-7.38%	-11.49%	-3.07%	**0.001**
		NPSnotMBI	-4.36%	-8.43%	-0.11%	**0.045**
	p-tau/Aβ42	MBI	16.18%	6.83%	26.35%	**<0.001**
		NPSnotMBI	5.93%	-2.24%	14.78%	0.159
	t-tau/Aβ42	MBI	14.10%	5.71%	23.16%	**0.001**
		NPSnotMBI	4.85%	-2.54%	12.80%	0.203
	Outcome	**Predictor**	**Standardized β**	**95% CI**		**p-value**
				Lower	Upper	
MEMENTO	Aβ42	MBI	-5.83%	-11.32%	-0.02%	**0.049**
		NPSnotMBI	-0.94%	-7.43%	6.00%	0.783
	Aβ40	MBI	-4.19%	-9.03%	0.91%	0.105
		NPSnotMBI	-1.55%	-7.16%	4.39%	0.599
	p-tau	MBI	7.98%	0.82%	15.65%	**0.028**
		NPSnotMBI	2.30%	-5.33%	10.55%	0.563
	t-tau	MBI	9.17%	-1.17%	20.59%	0.084
		NPSnotMBI	4.89%	-6.27%	17.37%	0.403
	Aβ42/40	MBI	-1.72%	-8.56%	5.64%	0.636
		NPSnotMBI	0.62%	-7.26%	9.17%	0.881
	p-tau/Aβ42	MBI	14.68%	3.27%	27.34%	**0.011**
		NPSnotMBI	3.27%	-8.26%	16.25%	0.592
	t-tau/Aβ42	MBI	15.93%	1.51%	32.40%	**0.029**
		NPSnotMBI	5.88%	-8.87%	23.02%	0.453

Beta coefficients represent the estimate percent difference in the CSF marker compared to the noNPS groups. Models adjusted for age, sex, education, and source of NPS

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Table 3 Association between NPS group and CSF biomarkers in a span of 4 years using linear mixed effect models

	Outcome	Predictor	Standardized β	95% CI		p-value
				Lower	Upper	
ADNI	Aβ42	MBI	-2.21%	-3.33%	-1.09%	**<0.001**
		NPSnotMBI	-0.003%	-0.50%	0.50%	0.990
	Aβ40	MBI	0.02%	-0.74%	0.79%	0.957
		NPSnotMBI	-0.10%	-0.48%	0.30%	0.633
	p-tau	MBI	2.65%	1.43%	3.89%	**<0.001**
		NPSnotMBI	0.38%	-0.007%	0.77%	0.055
	t-tau	MBI	2.28%	1.20%	3.37%	**<0.001**
		NPSnotMBI	0.44%	0.01%	0.86%	**0.045**
	Aβ42/40	MBI	-2.27%	-3.23%	-1.29%	**<0.001**
		NPSnotMBI	-0.0004%	-0.30%	0.30%	0.998
	p-tau/Aβ42	MBI	4.77%	2.83%	6.76%	**<0.001**
		NPSnotMBI	0.06%	-0.37%	0.48%	0.796
	t-tau/Aβ42	MBI	4.37%	2.61%	6.15%	**<0.001**
		NPSnotMBI	0.05%	-0.38%	0.47%	0.819
	Outcome	**Predictor**	**Standardized β**	**95% CI**		**p-value**
				Lower	**Upper**	
MEMENTO	Aβ42	MBI	-0.79%	-1.86%	0.30%	0.163
		NPSnotMBI	0.02%	-0.84%	0.89%	0.971
	Aβ40	MBI	-0.45%	-1.33%	0.43%	0.325
		NPSnotMBI	-0.74%	-1.54%	0.03%	0.067
	p-tau	MBI	1.47%	0.25%	2.72%	**0.022**
		NPSnotMBI	-0.26%	-0.74%	0.21%	0.293
	t-tau	MBI	1.69%	-0.08%	3.49%	0.067
		NPSnotMBI	-0.41%	-1.19%	0.35%	0.298
	Aβ42/40	MBI	-0.31%	-1.57%	0.96%	0.636
		NPSnotMBI	0.75%	-0.33%	1.87%	0.185
	p-tau/Aβ42	MBI	2.17%	0.23%	4.16%	**0.033**
		NPSnotMBI	-0.47%	-1.53%	0.58%	0.390
	t-tau/Aβ42	MBI	2.61%	0.18%	5.12%	**0.040**
		NPSnotMBI	-0.40%	-1.60%	0.78%	0.516

Beta coefficients represent the estimate percent difference in the CSF marker compared to the noNPS groups. Models adjusted for age, sex, education, and source of NPS

Cox regression showed that individuals with MBI had a 3.93-fold greater rate of incident dementia from MCI; NPSnotMBI had a 1.83-fold greater rate, not significantly different from noNPS. Of the dementia progressors in the MEMENTO sample, 34/42 (81.0%) developed AD dementia, 3/42 (7.1%) developed Lewy body dementia, 2/42 (4.8%) developed mixed dementia, and 3/42 (7.1%) had unknown dementia subtype.

Discussion
In this 4-year study of 510 participants with MCI, both the ADNI test sample and the MEMENTO validation sample demonstrated that MBI was cross-sectionally associated with AD biomarkers, and longitudinally associated with changes in these biomarkers, consistent with AD. Further, survival analyses found MBI to have a higher incidence rate of dementia than comparator groups and in the MEMENTO sample, 81% of dementia progressors developed AD. These findings demonstrate that applying the MBI criteria to MCI improves identification of individuals with positive AD biomarkers who are at higher risk for progression to AD dementia.

Cross sectional analysis
Across studies, MBI was associated with biomarker profiles consistent with prodromal AD. The one exception was MEMENTO in which there was no association with lower Aβ42/40 ratio, driven by lower Aβ40 levels (standardized β, -4.19% in MBI; -1.55% in NPSnotMBI). These Aβ40 differences were not seen in ADNI (standardized β, + 2.00% in MBI; -0.26% in NPSnotMBI). Possible explanations for lower Aβ40 include the presence of neuroinflammation [33] or amyloid angiopathy [34], and nicotine exposure [35]. Participant selection differences between studies may account for the divergent Aβ40 results. ADNI inclusion criteria are more restrictive, e.g., with respect to concurrent vascular burden[36]. MEMENTO is a study of real-world memory clinic patients, more heterogeneous than ADNI; participants likely had a greater vascular disease burden [37], and possibly higher nicotine
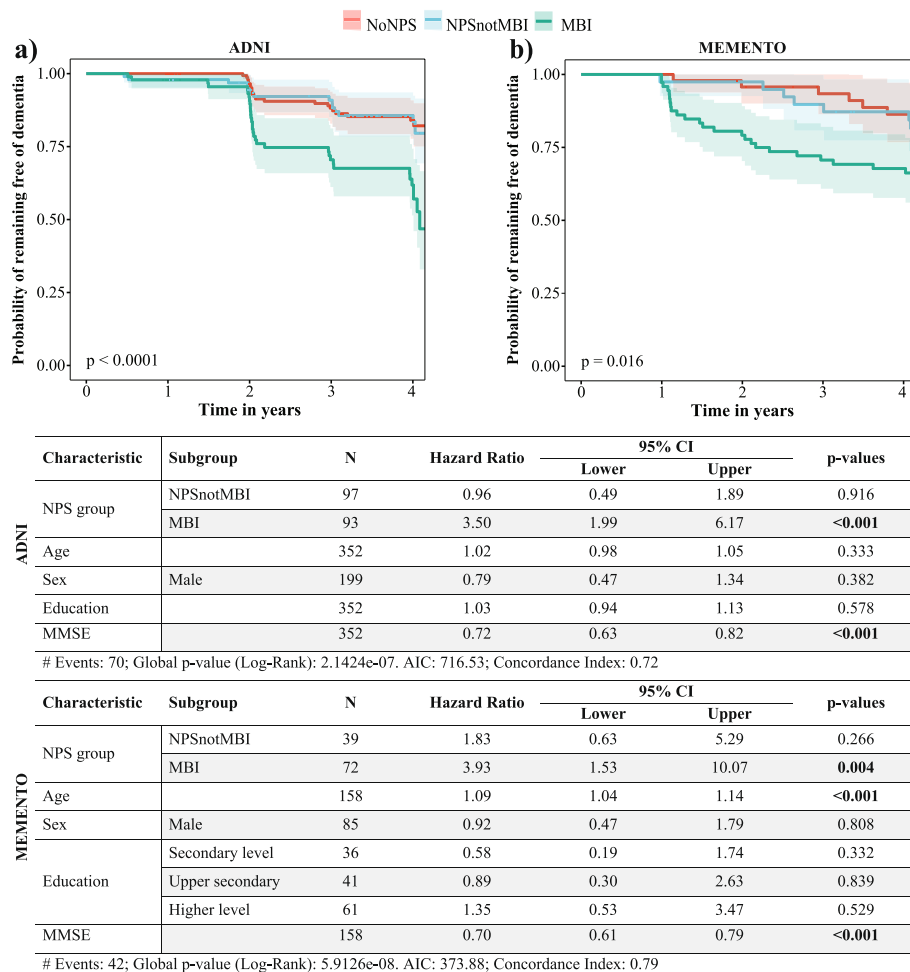
Fig. 2 Kaplan-Meir curve and Cox proportional hazards ratios for incident dementia

use. Thus, MEMENTO may harbor more potential contributors to lower Aβ40.

On the other hand, previous research has found a significant relationship between lower Aβ40 and a more rapid annual decline in MMSE in AD progressors [38, 39]. It has been hypothesized that those with low levels of Aβ40 may have more advanced amyloid plaque pathology, sequestering both Aβ42 and Aβ40 [39]. The Kaplan–Meier survival curves show a faster separation of MBI from the other two groups in MEMENTO vs ADNI, in line with the Aβ40 hypothesis. More research into this finding is required, however, the similarity between ADNI and MEMENTO for the remainder of the findings is reassuring.

In contrast, NPSnotMBI was only associated with lower Aβ42/40 ratio in ADNI. Although, the standardized β-coefficient for the ADNI Aβ42 level was comparable to MBI (-4.61% vs -5.52%), despite not meeting the threshold for significance. P-tau levels were substantially different (standardized β, + 9.67% in MBI, + 1.09% in NPSnotMBI). The NPSnotMBI group may include persons

with behavioral and cognitive symptoms secondary to life stressors or other causes, who are less likely to harbor AD. This finding accords with a previous systematic review of CSF studies in NPS, suggesting that noise in NPS measurement may result in inconsistent results [40].

The few previous cross-sectional studies on biomarker associations with MBI have been more consistent, although none were completed in an exclusively MCI sample. The Canadian TRIAD study and the Swedish BioFINDER2 study converged regarding MBI associations with biomarkers in CN participants. TRIAD demonstrated a correlation between MBI severity and greater global and striatal amyloid-PET tracer binding; Biofinder2 demonstrated associations between MBI and entorhinal and hippocampal tau-PET tracer uptake, and elevated CSF tau in amyloid positive participants [26, 27]. This finding was very recently replicated with plasma p-tau181 [41]. Another study, in a mixed sample of NC and MCI participants, reported an association between lower plasma Aβ42/Aβ40 ratio and higher MBI score [28]. These findings are congruent with the a priori development

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goal of MBI to increase signal and reduce noise when using NPS to identify preclinical and prodromal AD [12, 42].

The MBI-related differences in p-tau/Aβ42 and t-tau/Aβ42 in ADNI and MEMENTO are meaningful. These ratios are important biomarkers for detecting prodromal AD in MCI, and for AD prognostication. Both p-tau/Aβ42 and t-tau/Aβ42 ratios have demonstrated high concordance with amyloid PET classification, predicting greater 2-year clinical decline in patients with MCI [43]. A recent study that included all three CSF markers determined p-tau/Aβ42 as the most accurate predictor of imminent progression to AD (sensitivity 82.9%, specificity 90%) over a mean time of 26.07 months [44]. Thus, the biomarker profiles from both ADNI and MEMENTO align with AD-related changes for amyloid, tau, and neurodegeneration in association with MBI but not with the comparator groups. These findings support a biological basis for the NPS that meet MBI criteria, the inclusion of MBI in the ATN framework, and the utility of the MBI criteria for identifying prodromal AD.

Longitudinal analyses – LME models

That MBI in MCI was associated with AD-related changes over 4 years, while NPSnotMBI was not, is an important and novel finding. Longitudinal data for MBI and AD biomarkers in dementia-free individuals are scarce, and absent in an MCI-only sample. A mixed CN/MCI ADNI study reported an association between MBI and a 2-year increase in plasma neurofilament light, a marker of axonal loss or neurodegeneration [45]. Very recently, a related study utilizing ADNI plasma p-tau181 samples found a similar increase in p-tau over time in association with MBI, as well as greater decline in memory and executive function, vs noNPS and NPSnotMBI comparators [41]. Our CSF study across two independent cohorts is the most definitive evidence thus far, demonstrating that refining NPS measurement can enrich samples for AD. In our study, longitudinal results were not identical in ADNI and MEMENTO. In fact, we would not expect them to be. ADNI is a restricted cohort that mimics a clinical trial and MEMENTO comprises real world memory clinic patients – we would expect more heterogeneity in MEMENTO. Further, due to the smaller sample size in MEMENTO, the MBI estimate was not precise enough to statistically differ from NPS-not-MBI, despite the difference in magnitude and direction.

Survival analyses – Kaplan–Meier and Cox regressions

Across ADNI and MEMENTO, dementia-free survival was significantly lower in the MBI group versus the NPSnotMBI and noNPS groups. Cox regressions demonstrated that MBI had a significantly and substantially higher rate of incident dementia compared to noNPS, while NPSnotMBI did not differ from noNPS. These survival analysis results conform with the findings from the cross-sectional and longitudinal biomarker analyses. Findings also align with the bulk of the MBI literature comprising epidemiological or cohort studies with MBI as exposure, and outcomes of cognition, function, or risk marker. Consistently, whether in CN, MCI, or mixed dementia-free samples, or whether in clinical, community, or even online cohort studies, the data have consistently shown that selecting NPS in accordance with MBI criteria identifies a group with greater baseline risk [37, 46–52], and/or greater risk for incident MCI and dementia [12–20, 41, 53, 54] than the comparator groups.

The current study extends previous work to demonstrate clear associations between MBI and the full palette of CSF biomarkers in the NIA-AA research framework for AD [11]. However, the translation to clinical care or clinical trial recruitment is imperative. In these observational cohorts, we operationalized the MBI cardinal criteria of de novo symptom emergence in later life and symptom persistence for ≥ 6 months by 1) including only participants with no formal psychiatric and neurodevelopmental conditions; and 2) ensuring NPS were present at two consecutive visits. This approach is feasible in research cohorts, where multiple visits are available for selection and stratification, but not at an initial clinic visit or clinical trial screening assessment.

Single-visit alternatives to implement MBI criteria are required. In anticipation of this issue, ISTAART developed the mild behavioral impairment checklist (MBI-C) as the case ascertainment instrument to measure MBI in accordance with the criteria. The MBI-C assesses NPS across the domains of MBI, with explicit stipulations that symptoms represent change and persist, language echoed in the ATN framework [11]. Multiple validations of the MBI-C have been published [55–63], and it has been used in several published epidemiological and biomarker studies [14, 18, 19, 26, 27, 49, 51, 62, 64]. However, more research is required, and the methods used in the current study need replication in different and more diverse cohorts using the MBI-C as the NPS measure. However, our findings are novel and meaningful, for the first time showing clear associations between MBI in MCI and cross-sectional and longitudinal CSF-measured ATN biomarkers, supporting the utility of MBI to improve specificity of MCI in detection of prodromal AD [13]. The clinical translation of these findings would be to include an assessment of MBI (e.g., MBI-C at a single

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clinic visit or NPI over two clinic visits) in conjunction with a standard measure of cognition (e.g., MMSE). The presence of MBI would influence the interpretation of the cognitive measure and change the estimate for presence of AD biomarkers at the time of the visit, and the potential change of the biomarkers and cognition over time.

Limitations

MBI symptoms were based on NPI-measured NPS at study visits. Transient symptoms present only within the one-month reference range preceding the visit could be included in MBI case status, resulting in false positives. Conversely, the breadth of MBI symptoms and behaviors may not have been captured with the current approach, resulting in false negatives. Both types of errors could reduce the magnitude of effect. The exclusion of participants with a history of psychiatric conditions could also be a limitation, especially if symptoms were of relatively recent onset but still diagnosed as formal psychiatric conditions. It is conceivable that some of these excluded participants had MBI rather than a psychiatric disorder. Our MBI case status reflected global NPS burden, rather than individual MBI domains (i.e., apathy, affect, impulsivity, social inappropriateness, and psychosis). Persistent NPS using our operational definition could consist of symptoms from different domains. Subsequent domain-specific analyses are required, which will require substantially larger samples. Finally, while ADNI and MEMENTO are similar enough to compare in this analysis, different inclusion criteria, participant characteristics, and comorbidities could confound the relationship between NPS status and biomarkers. Nonetheless, the similarities are reassuring.

Conclusions

Mental health symptoms are important links to cognitive health and better assessment and classification of these symptoms can result in more accurate dementia detection. Our findings suggest AD proteinopathies may be part of the neurobiology of later-life onset and persistent NPS that meet MBI criteria. The finding that 81% of MBI progressors to dementia developed AD support the continued inclusion of MBI in the ATN framework and clinical staging. Results are congruent with the a priori goals in development of the MBI criteria and have implications for research methodology, clinical trial recruitment, drug development, and clinical care.

Appendix

Table 4 A list of Memento collaborators

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Abbreviations

AD	Alzheimer disease
CSF	Cerebrospinal fluid
ATN	Amyloid Tau Neurodegeneration
PET	Positron emission tomography
MCI	Mild cognitive impairment
NPS	Neuropsychiatric symptoms
MBI	Mild behavioral impairment
NPSnotMBI	NPS not meeting MBI criteria
CN	Cognitively normal / normal cognition
MMSE	Mini Mental State Exam
LME	Linear mixed effects
NPI	Neuropsychiatric Inventory
Aβ	myloid beta
p-tau	hyperphosporylated tau
t-tau	total tau

Declarations

Ethics approval and consent to participate

For both ADNI and MEMENTO, ethics approval was obtained from the review boards of the participating institutions. Informed consent was obtained from every participant prior to enrollment.

Consent for publication

All authors have approved the contents of this manuscript and provided consent for publication.

Competing interests

HC, RL, SN, PR report no conflicts. ES has received consulting fees from Eli Lilly. ZI has received consulting fees from Otsuka/Lundbeck, outside the submitted work. His insti-tution has received funds from Biogen and Roche, also outside the submitted work.

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