Mild Behavioral Impairment (MBI), Prognosis, Biomarkers

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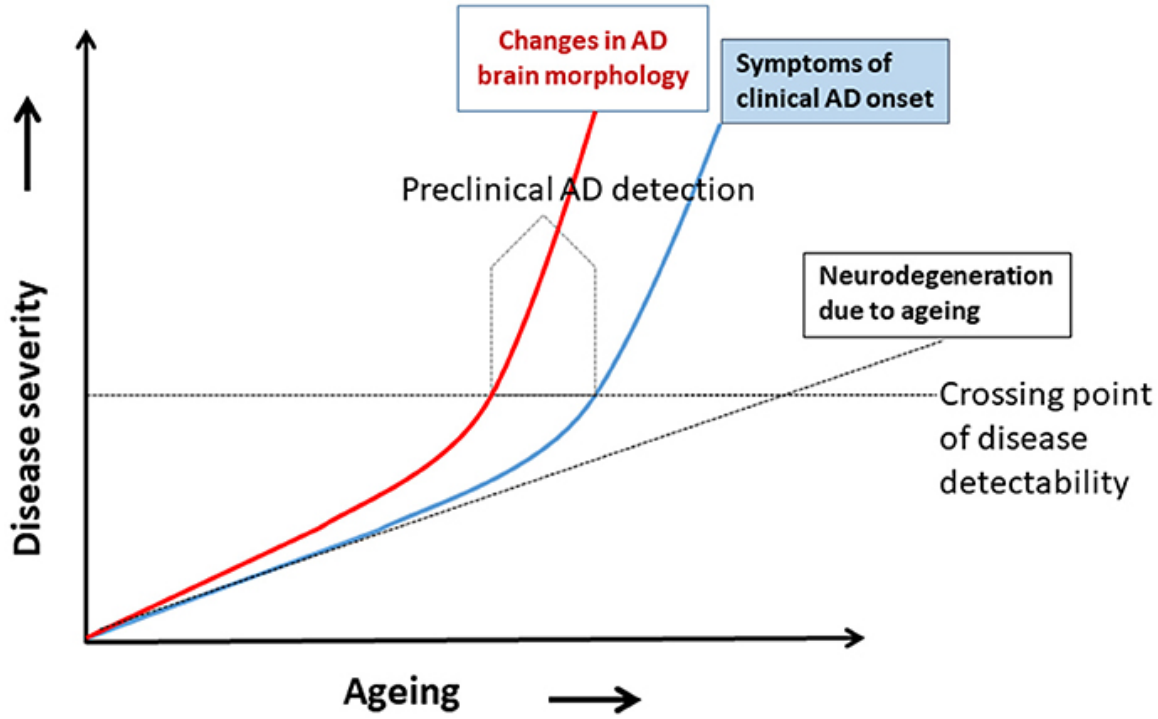
Current status and needs

- We need to detect more precisely individuals with preclinical and prodromal AD
- Research on disease modifying therapies has intensified this need



Khan 2018

We have a *cognocentric* model of dementia

- **Start with AD** – cognitive (memory) and functional loss
- **Mild Cognitive Impairment** (prodromal AD in some)
  - A transitional state between normal aging and dementia
  - Cognitive decline but essentially normal function
- **Subjective Cognitive Decline** (preclinical AD in some)
  - Subjective cognitive symptoms absent objective findings
- **Normal Cognition** (preclinical AD in some)

Every step further away from AD is associated with less signal and more noise

Can we leverage behaviour, like depression, for example to improve AD detection?

Well that didn't quite work out. But depression is in all the prediction models. What are we doing wrong?

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Cerebrospinal Fluid Correlates of Neuropsychiatric Symptoms in Patients with Alzheimer's Disease/Mild Cognitive Impairment: A Systematic Review

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Table 2
This table classifies the association status of each NPS from each study into one of the 3 categories. Number of studies done for each NPS are indicated. Number in the parenthesis reflect the total number of AD/MCI patients when all the studies were combined. The last column also indicates the total number of different measurement methods used for each NPS

NPS	No association	Association in favor of AD pathology	Association NOT in favor of AD pathology	# of NPS measurement methods
Depression	5 studies (585)	1 study (110)	3 studies (452)	7
Sleep/night time behavior	6 studies (692)	2 studies (130)	-	4
Hallucinations/delusions/psychosis	5 studies (732)	2 studies (193)	–	2
Anxiety	2 studies (219)	2 studies (334)	–	3
Agitation/Aggression	–	4 studies (520)	–	3
Eating/appetite/low BMI	2 studies (368)	3 studies (901)	–	2
Apathy	2 studies (567)	2 studies (331)	–	1
Irritability	–	1 study (268)	–	1
Elation/Euphoria	–	-	–	-
Disinhibition	–	–	–	–
Motor disturbances	–	–	–	–

Total # of patients = 3,063, Total # of AD patients = 1,340 (44%), Total # of MCI patients = 1,723 (56%).

Maybe a cross-sectional measurement isn't good enough

N= ~56,000 patients (27,948 matched pairs)

History of mood disorder associated with a higher likelihood of developing AD (OR=1.17) in the 5-year but not the 10-year window

Some of the mood syndromes were likely misdiagnosed AD

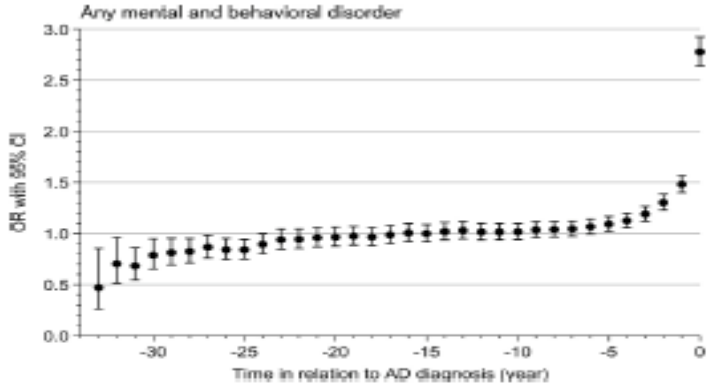

Fig. 1. The association between any mental and behavioral disorder (ICD-10 codes F00–F99) and Alzheimer's disease (AD) with different time windows between exposure and outcome. Number of exposed persons is calculated cumulatively at each time point.

Studies like this suggest that the later in life the *emergence* of psychiatric symptomatology, the more likely these symptoms represent the beginnings of a neurodegenerative process

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Original article

Hospital-treated mental and behavioral disorders and risk of Alzheimer's disease: A nationwide nested case-control study

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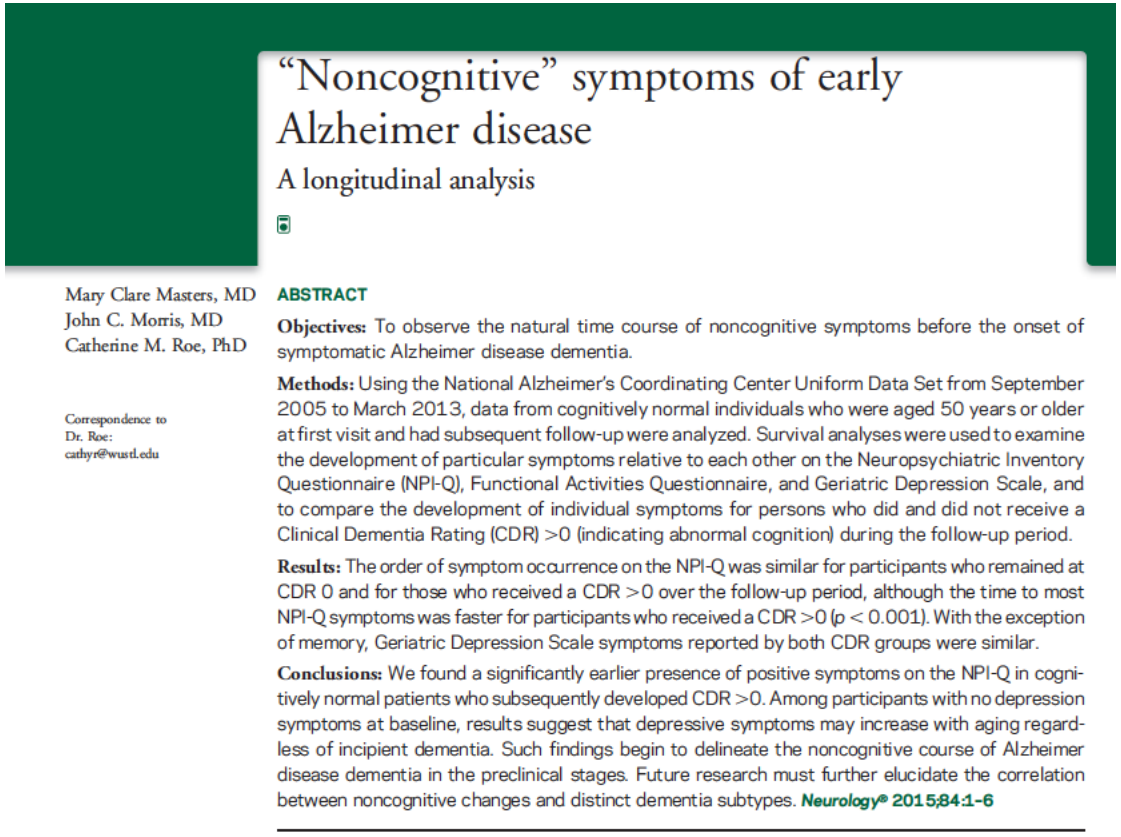
ABSTRACT

Background: Studies investigating psychiatric disorders as Alzheimer's disease (AD) risk factors have yielded heterogeneous findings. Differences in time windows between the exposure and outcome could be one explanation. We examined whether (1) mental and behavioral disorders in general or (2) specific mental and behavioral disorder categories increase the risk of AD and (3) how the width of the time window between the exposure and outcome affects the results.
Methods: A nationwide nested case-control study of all Finnish clinically verified AD cases, alive in 2005 and their age, sex and region of residence matched controls (n of case-control pairs 27,948). History of hospital-treated mental and behavioral disorders was available since 1972.
Results: Altogether 6.9% (n = 1932) of the AD cases and 6.4% (n = 1784) of controls had a history of any mental and behavioral disorder. Having any mental and behavioral disorder (adjusted OR = 1.07, 95% CI = 1.00–1.16) or depression/other mood disorder (adjusted OR = 1.17, 95% CI = 1.05–1.30) were associated with higher risk of AD with 5-year time window but not with 10-year time window (adjusted OR, 95% CI 0.99, 0.91–1.08 for any disorder and 1.08, 0.96–1.23 for depression).
Conclusions: The associations between mental and behavioral disorders and AD were modest and dependent on the time window. Therefore, some of the disorders may represent misdiagnosed prodromal symptoms of AD, which underlines the importance of proper differential diagnostics among older persons. These findings also highlight the importance of appropriate time window in psychiatric and neuroepidemiology research.

Neuropsychiatric symptoms: core AD features

Earlier presence of NPS in NC who went on to develop a CDR>0



"Noncognitive" symptoms of early Alzheimer disease

A longitudinal analysis

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ABSTRACT

Objectives: To observe the natural time course of noncognitive symptoms before the onset of symptomatic Alzheimer disease dementia.

Methods: Using the National Alzheimer's Coordinating Center Uniform Data Set from September 2005 to March 2013, data from cognitively normal individuals who were aged 50 years or older at first visit and had subsequent follow-up were analyzed. Survival analyses were used to examine the development of particular symptoms relative to each other on the Neuropsychiatric Inventory Questionnaire (NPI-Q), Functional Activities Questionnaire, and Geriatric Depression Scale, and to compare the development of individual symptoms for persons who did and did not receive a Clinical Dementia Rating (CDR) >0 (indicating abnormal cognition) during the follow-up period.

Results: The order of symptom occurrence on the NPI-Q was similar for participants who remained at CDR 0 and for those who received a CDR >0 over the follow-up period, although the time to most NPI-Q symptoms was faster for participants who received a CDR >0 ($p < 0.001$). With the exception of memory, Geriatric Depression Scale symptoms reported by both CDR groups were similar.

Conclusions: We found a significantly earlier presence of positive symptoms on the NPI-Q in cognitively normal patients who subsequently developed CDR >0. Among participants with no depression symptoms at baseline, results suggest that depressive symptoms may increase with aging regardless of incipient dementia. Such findings begin to delineate the noncognitive course of Alzheimer disease dementia in the preclinical stages. Future research must further elucidate the correlation between noncognitive changes and distinct dementia subtypes. **Neurology® 2015;84:1–6**

59% developed NPS before a cognitive diagnosis including *30% of those who developed Alzheimer disease*

Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers

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Abstract

Introduction: Neuropsychiatric symptoms (NPSs) are nearly universal in cognitive disorders. The mild behavioral impairment construct postulates that NPS may be the first symptom of impending dementia.

Methods: Participants were cognitively normal volunteers followed up approximately annually at Alzheimer's Disease Centers, who were assessed on the Neuropsychiatric Inventory and had at least one follow-up visit during which they were diagnosed with mild cognitive impairment (MCI) or dementia. Descriptive statistics were used to determine sequencing of NPS presence with cognitive diagnoses.

Results: Data were available for 1998 participants who progressed to MCI or dementia. Over 59% developed NPS before the diagnosis of any cognitive disorder. Depression and irritability were the most common NPSs to precede cognitive diagnoses (24 and 21%, respectively).

Discussion: NPSs precede a cognitive diagnosis in most people who develop cognitive decline, both MCI and dementia. These individuals are an important group to focus clinical and research efforts.

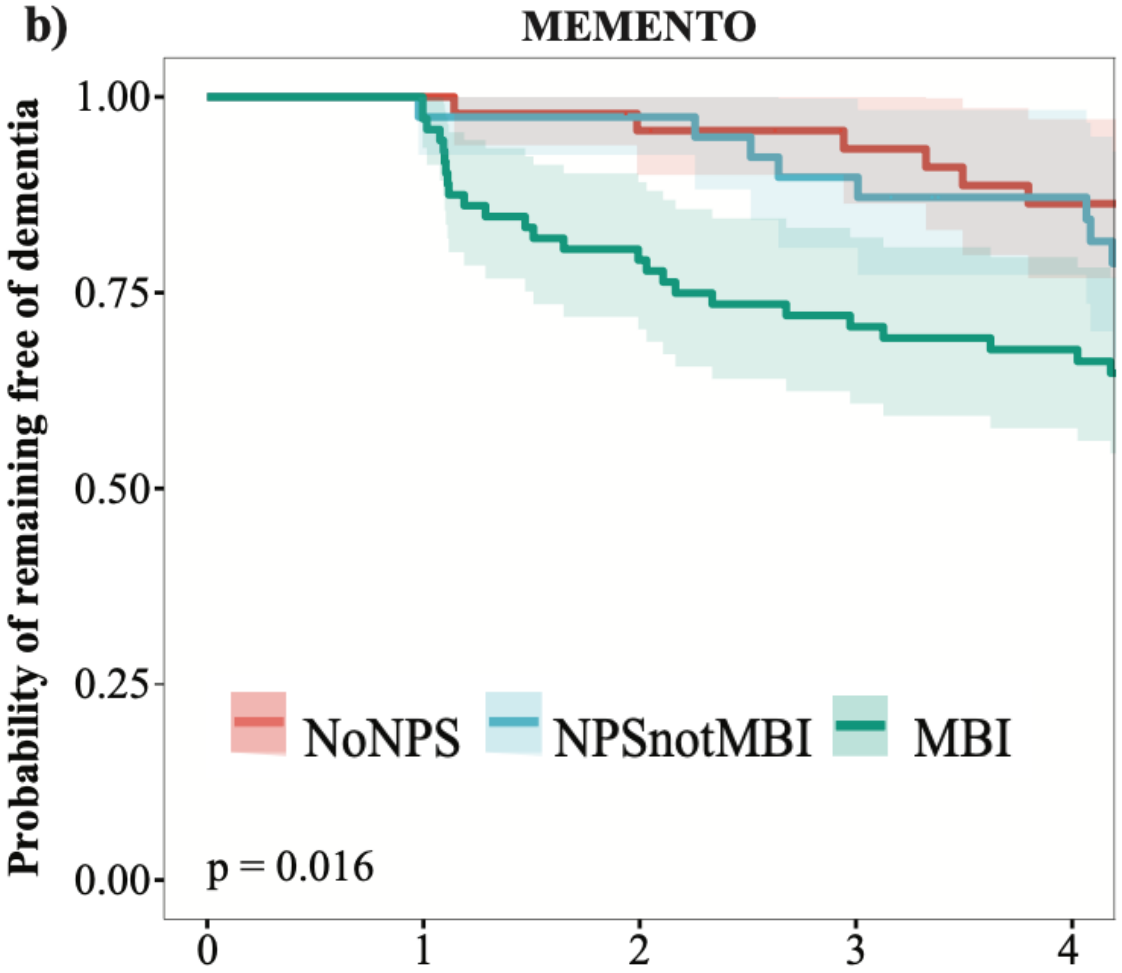
Keywords: Neuropsychiatric symptoms; Dementia; Mild cognitive impairment; Alzheimer's and related dementias; Mild behavioral impairment

Mild Behavioral Impairment (MBI): rationale

- Describe later onset NPS as a preclinical / prodromal syndrome **of all dementias**, and not just bvFTD, with clear operationalized criteria
- Explicitly define relationship between MBI and MCI (***not competing constructs***)
- Standardize the assessment to help define and identify early the target population
- Develop novel treatments based on these targets

- Change in behavior or personality with **emergence** ≥ age 50 and **persistence** for ≥6 months
- Five domains
  - Drive and Motivation (apathy)
    - Sherman et al. 2018, Vellone 2022
  - Affective Dysregulation (mood/anxiety)
    - Ismail et al. 2018, Ebrahim 2023
  - Impulse Dyscontrol (agitation, impulsivity, response inhibition)
    - Bateman et al. 2020, Saari et al. 2021, Gill et al. 2021
  - Social Inappropriateness (social cognition)
    - Desmarais et al. 2018
  - Thoughts and Perception (psychosis)
    - Fischer and Aguera-Ortiz 2018, Ismail 2023
    - Fischer et al. 2019 – ISTAART Psychosis in AD criteria

To persist or not to persist - MBI and incident dementia: In MCI, *persistent* NPS have shorter dementia-free survival than impersistent NPS



Characteristic	Subgroup	N	Hazard Ratio	95% CI		p-values
				Lower	Upper	
NPS group	NPSnotMBI	39	1.83	0.63	5.29	0.266
	MBI	72	3.93	1.53	10.07	**0.004**

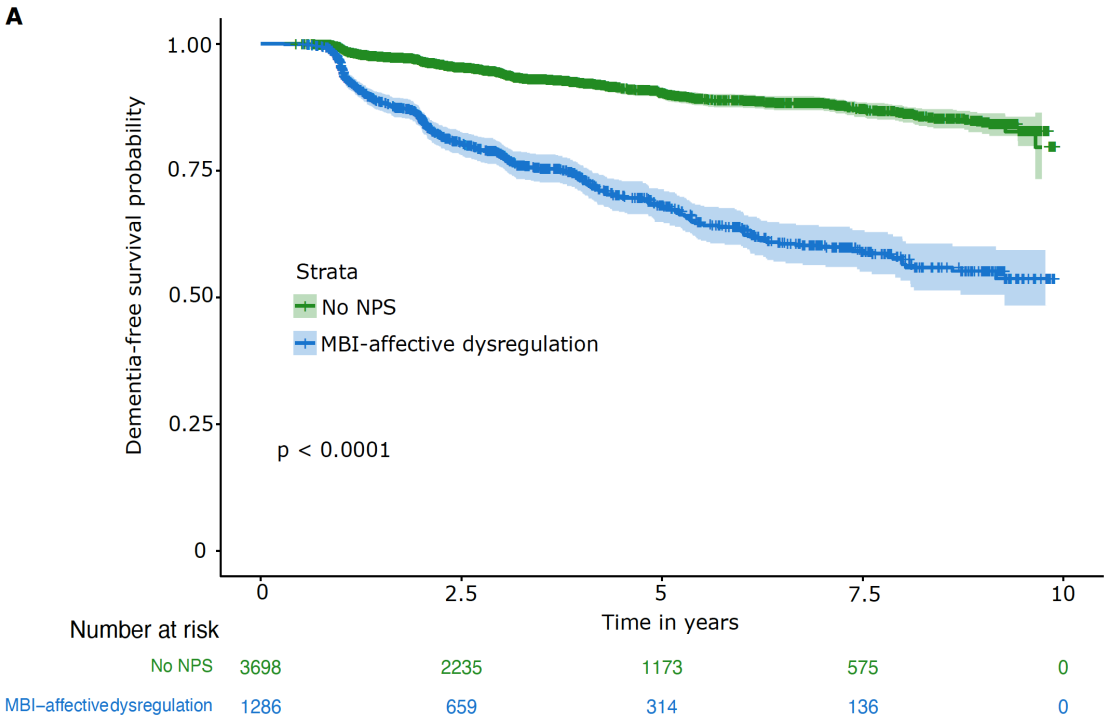
In MCI, *persistent* NPS have shorter dementia-free survival than impersistent NPS

Of MBI progressors to dementia, 81% developed AD dementia

Ismail 2023 – under review

Back to “depression”

Emergent and *persistent* mood sx



- HR incident dementia 1.76 (CI: 1.48-2.08)
- Of MBI-affect converters to dementia, 85.5% developed AD, which increased to 91.4% in aMCI

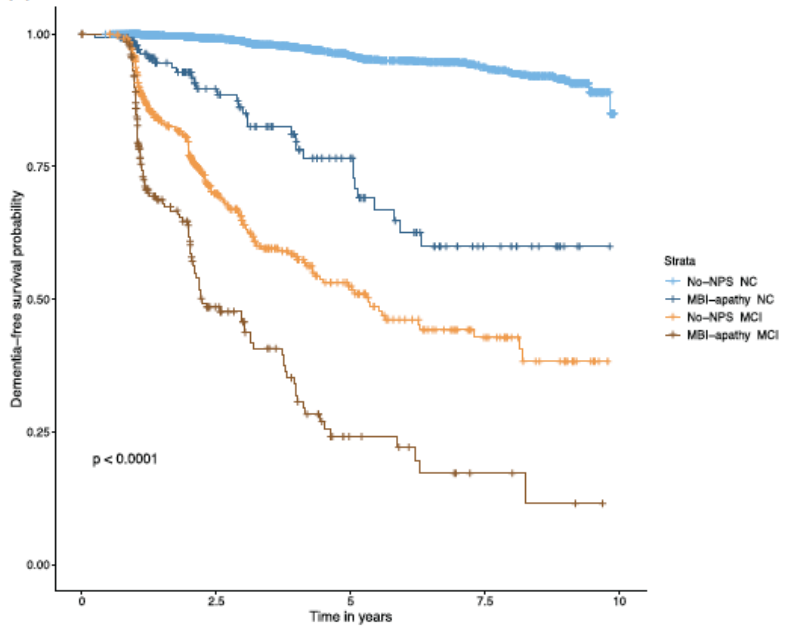
Ebrahim et al. 2023 J Affect Dis

Apathy

(A)

Clinical cognitive diagnosis	No-NPS	MBI-apathy	Effect of apathy within the strata of clinical cognitive diagnosis
	HR (95% CI) *p*-value	HR (95% CI) *p*-value	HR (95% CI) *p*-value
NC	1 (Reference)	5.91 (3.91, 8.93) $p<0.001$	5.91 (3.91, 8.93) $p<0.001$
MCI	13.81 (10.66, 17.89) $p<0.001$	29.83 (22.27, 39.96) $p<0.001$	2.16 (1.69, 2.77) $p<0.001$
Multiplicative interaction test:		HR=2.73, 95%CI:1.69-4.42, $p<0.001$	

(B) HR=2.69

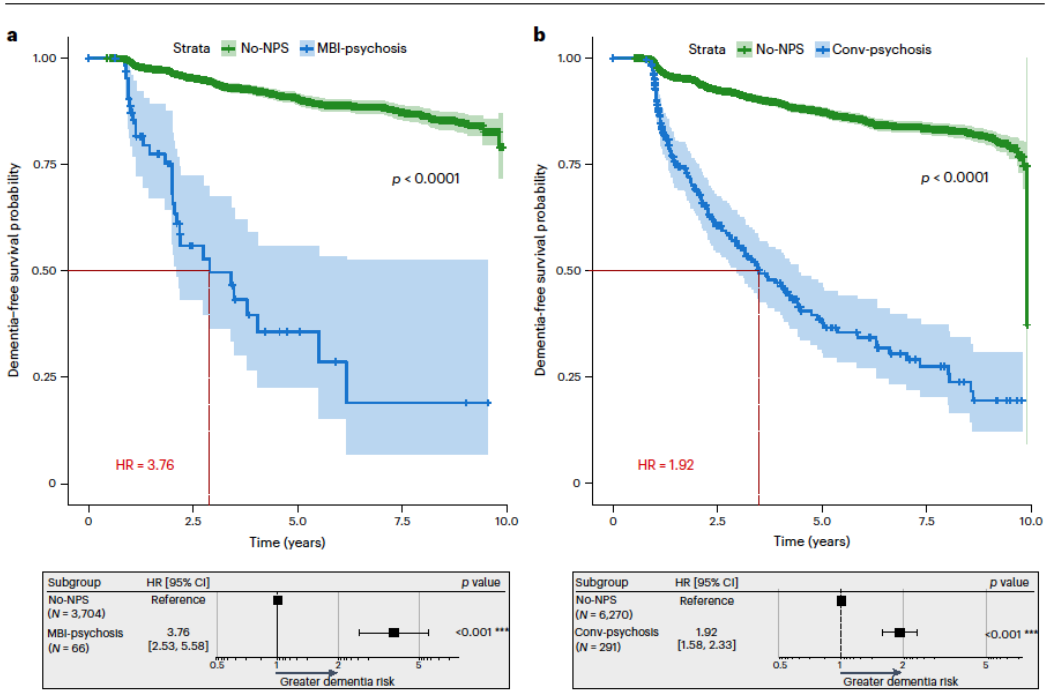


MBI-Apathy progressors: 80.9% AD; 4.3% bvFTD; 5.0% DLB

Vellone 2022

Psychosis

Cognitive status	No-NPS	MBI-psychosis	Effect of psychosis within the strata of cognitive status
	HR [95% CI] *p* value	HR [95% CI] *p* value	HR [95% CI] *p* value
NC	1 [Reference]	9.96 [3.65, 27.22] **$p<0.001$**	9.96 [3.65, 27.22] **$p<0.001$**
MCI	13.34 [10.32, 17.24] **$p<0.001$**	45.09 [28.68, 70.91] **$p<0.001$**	3.38 [2.22, 5.15] **$p<0.001$**
Multiplicative interaction test		HR=2.95, CI: 0.99–8.72, **$p=0.05$**	



MBI-Psychosis progressors: 66.7% AD; 0% bvFTD; 10.0% DLB

Ismail 2023

Adding behavioural risk to cognitive risk improves specificity of SCD to predict incident MCI

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Mild Behavioral Impairment and Subjective Cognitive Decline Predict Cognitive and Functional Decline

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Abstract.
Background: Mild behavioral impairment (MBI) and subjective cognitive decline (SCD) are dementia risk states, and potentially represent neurobehavioral and neurocognitive manifestations, respectively, of early stage neurodegeneration. Both MBI and SCD predict incident cognitive decline and dementia, are associated with known dementia biomarkers, and are both represented in the NIA-AA research framework for AD in Stage 2 (preclinical disease).
Objective: To assess the associations of MBI and SCD, alone and in combination, with incident cognitive and functional decline in a population of older adults. We tested the hypothesis that MBI and SCD confer additive risk for decline.
Methods: Cognitively normal participants were followed up annually at Alzheimer's Disease Centers. Logistic regression assessed the relationship between baseline classification (MBI-SCD-, MBI-SCD+, MBI+SCD-, or MBI+SCD+) and 3-year outcome.
Results: Of 2,769 participants (mean age=76), 1,536 were MBI-SCD-, 254 MBI-SCD+, 743 MBI+SCD-, and 236 MBI+SCD+. At 3 years, 349 (12.6%) declined to CDR>0, including 23.1% of the MBI+ group, 23.5% of the SCD+ group, and 30.9% of the intersection group of both MBI+and SCD+ participants. Compared to SCD-MBI-, we observed an ordinal progression in risk (ORs [95% CI]): 3.61 [2.42–5.38] for MBI-SCD+ (16.5% progression), 4.76 [3.57–6.34] for MBI+SCD- (20.7%), and 8.15 [5.71–11.64] for MBI+SCD+(30.9%).
Conclusion: MBI and SCD together were associated with the greatest risk of decline. These complementary dementia risk syndromes can be used as simple and scalable methods to identify high-risk patients for workup or for clinical trial enrichment.

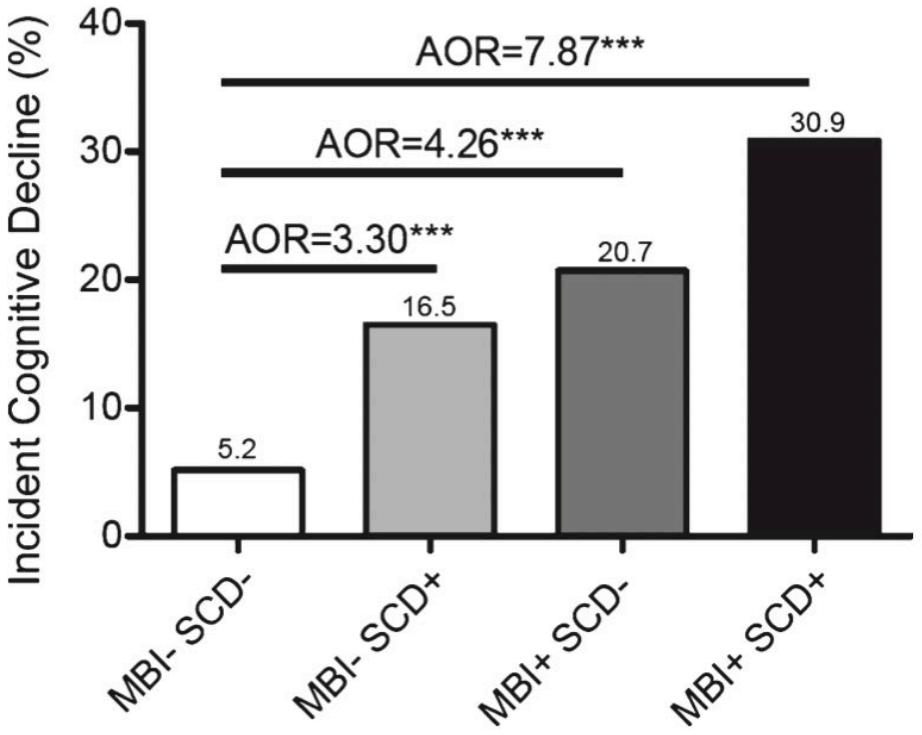

Fig. 3. Odds of CDR>0 after three years versus MBI/SCD grouping.

Adding behavioral risk to cognitive risk improves specificity of MCI to predict incident dementia

RESEARCH ARTICLE OPEN ACCESS

Progression to Dementia or Reversion to Normal Cognition in Mild Cognitive Impairment as a Function of Late-Onset Neuropsychiatric Symptoms

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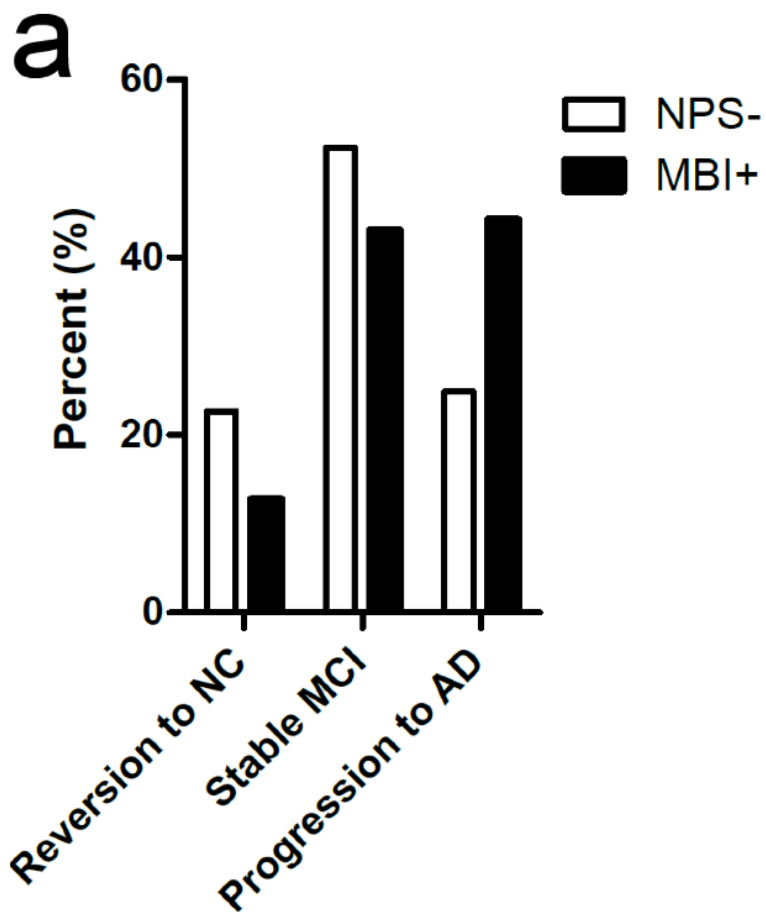
Abstract

Background and Objectives

Mild cognitive impairment (MCI) is an at-risk state for dementia; however, not all individuals with MCI transition to dementia, and some revert to normal cognition (NC). Here, we investigate whether mild behavioral impairment (MBI), the late-life onset of persistent neuropsychiatric symptoms (NPS), improves the prognostic specificity of MCI.

Methods

Participants with MCI from the National Alzheimer's Coordinating Center Uniform Data Set were included. NPS were operationalized with the Neuropsychiatric Inventory Questionnaire to identify participants without NPS and those with MBI (persistent, late-onset NPS). Individuals with late-onset NPS not meeting the MBI persistence criterion (NPS_NOT_MBI) were retained for secondary analyses. Progression to dementia, stable MCI, and reversion to NC after 3 years of follow-up were defined per National Institute on Aging–Alzheimer's Association and Petersen criteria.



MBI vs NPSnotMBI and plasma p-tau

RESEARCH ARTICLE

Plasma p-Tau181 and Neuropsychiatric Symptoms in Preclinical and Prodromal Alzheimer Disease

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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 4 Years Using Linear Mixed-Effects Models

Outcome	Predictor	β[a]	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–NPI-Q)	−0.0126	−0.06 to −0.035	0.60
	NPI/NPI-Q (NPI-Q)	−0.186	−0.433 to 0.06	0.14
	Years	0.0096	0.004 to 0.016	**0.002**

Abbreviations: MBI = mild behavioral impairment; MMSE = Mini-Mental State Examination; NPI/NPI-Q = Neuropsychiatric Inventory/Neuropsychiatric Inventory Questionnaire; NPS = neuropsychiatric symptom.
The model was adjusted for age, sex, education, MMSE, source of NPS data, and time. p-tau181 values were log transformed.
[a] β-coefficients represent the estimate percent difference in the plasma p-tau181 biomarker.

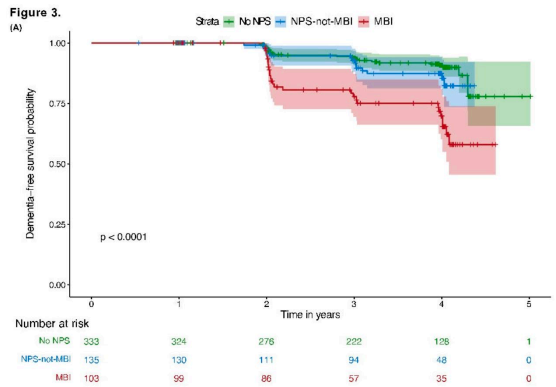
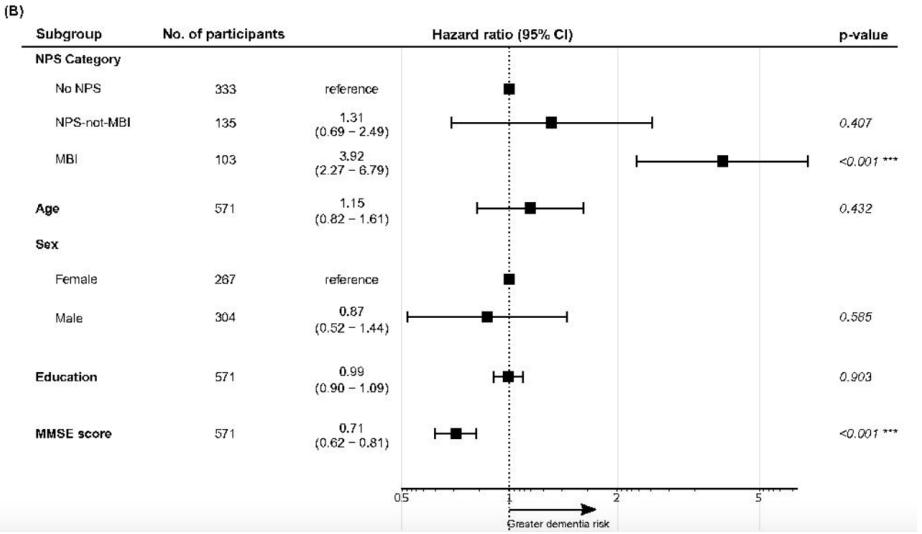


Table 4 Longitudinal Association Between Annual Measures of MBI (Between-Person NPS Changes) and NPS-Not-MBI (Within-Person NPS Changes) and Changes in Cognitive Task Performance Over 4 Years Using Linear Mixed-Effects Models

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

Abbreviations: MBI = mild behavioral impairment; NPS = neuropsychiatric symptom; RAVLT = Rey Auditory Verbal Learning Test.
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.



Ghahremani 2023

Cognitive Status: MCI
Behavioural Status: MBI, NPSnotMBI, and NoNPS

Cross-sectional models

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.

In Mild Cognitive Impairment, Mild Behavioral Impairment was associated with Alzheimer-related changes, including:

Lower Aβ42 and Aβ42/40, greater p-tau and tau, higher p-tau/Aβ42 and tau/Aβ42.

Longitudinal Models

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.

Estimates for CSF AD biomarkers in MCI participants differed based behavioural status. MBI performed better than conventionally measured NPS.

Ismail 2023 under review

MBI checklist: www.MBItest.org

Mild Behavioral Impairment Checklist (MBI-C)

Date: _____

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3
Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?	Yes	No	1 2 3
Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?	Yes	No	1 2 3
Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?	Yes	No	1 2 3
Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?	Yes	No	1 2 3
Does the person no longer find food tasteful or enjoyable? Are they eating less?	Yes	No	1 2 3
Does the person hoard objects when she/he did not do so before?	Yes	No	1 2 3
Has the person developed simple repetitive behaviors or compulsions?	Yes	No	1 2 3
Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?	Yes	No	1 2 3
This domain describes following societal norms and having social graces, tact, and empathy			
Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others' feelings?	Yes	No	1 2 3
Has the person started talking openly about very personal or private matters not usually discussed in public?	Yes	No	1 2 3
Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?	Yes	No	1 2 3
Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?	Yes	No	1 2 3
Does the person now talk to strangers as if familiar, or intrude on their activities?	Yes	No	1 2 3
This domain describes strongly held beliefs and sensory experiences			
Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?	Yes	No	1 2 3
Has the person developed suspiciousness about the intentions or motives of other people?	Yes	No	1 2 3
Does she/he have unrealistic beliefs about her/his power, wealth or skills?	Yes	No	1 2 3
Does the person describe hearing voices or does she/he talk to imaginary people or "spirits"?	Yes	No	1 2 3
Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	Yes	No	1 2 3

MBI-C is an optional assessment in NACC.

Validated for in-person, telephone, and online use

NIA-AA Framework and Clinical Staging

…perhaps less cognocentric and also includes MBI

The framework should stimulate efforts to develop new behavioral measures that monitor functioning in individuals with preclinical AD to determine how they align within ATN system.

An individual may be placed into stage 2 on the basis of neurobehavioral symptoms alone, that is, without evident cognitive decline. **To reflect this, we use the term "clinical staging" rather than cognitive staging** to recognize that early clinical manifestations of AD may be either cognitive or neurobehavioral.

NIA-AA Stage 2 (i.e., NC or SCD)

"(Stage 2) represents a change from individual baseline within past 1–3 years, and persistent for at least 6 months. Although cognition is the core feature, mild neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist. In some individuals, the primary complaint may be neurobehavioral rather than cognitive. Neurobehavioral symptoms should have a clearly defined recent onset, which persist and cannot be explained by life events."

NIA-AA Stage 3 (i.e., MCI)

"Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist."

Jack 2018, Knopman 2018