

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.

Results

The primary sample consisted of 739 participants (NPS– $n = 409$ and MBI+ $n = 330$; 75.16 ± 8.6 years old, 40.5% female). After 3 years, 238 participants (33.6%) progressed to dementia, and 90 (12.2%) reverted to NC. Compared to participants without NPS, participants with MBI were significantly more likely to progress to dementia (adjusted odds ratio [AOR] 2.13, 95% CI 1.52–2.99), with an annual progression rate of 14.7% (vs 8.3% for participants with MCI without NPS). Compared to participants without NPS, participants with MBI were less likely to revert to NC (AOR 0.48, 95% CI 0.28–0.83, 2.5% vs 5.3% annual reversion rate). The NPS_NOT_MBI group ($n = 331$, 76.5 ± 8.6 years old, 45.9% female) were more likely to progress to dementia (AOR 2.18, 95% CI 1.56–3.03, 14.3% annual progression rate) but not less likely to revert to NC than those without NPS. Accordingly, both NPS_NOT_MBI and MBI+ participants had lower Mini-Mental State Examination scores than NPS– participants after 3 years.

Discussion

Late-onset NPS improve the specificity of MCI as an at-risk state for progression to dementia. However, only persistent late-onset NPS are associated with a lower likelihood of reversion to NC, with transient NPS (i.e., NPS_NOT_MBI) not differing from the NPS– group. Clinical prognostication can be improved by incorporating late-onset NPS, especially those that persist (i.e., MBI), into risk assessments. Clinical trials may benefit from enrichment with these higher-risk participants with MCI.

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Glossary

AD = Alzheimer disease; **ADRC** = Alzheimer's Disease Research Center; **AOR** = adjusted odds ratio; **ISTAART-AA** = International Society to Advance Alzheimer's Research and Treatment–Alzheimer's Association; **MBI** = mild behavioral impairment; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NACC** = National Alzheimer's Coordinating Center; **NC** = normal cognition; **NPI-Q** = Neuropsychiatric Inventory Questionnaire; **NPS** = neuropsychiatric symptoms; **UDS** = Uniform Data Set.

The global prevalence of dementia is expected to more than triple by 2050.¹ Given that neural changes in individuals who go on to develop dementia occur up to 2 decades before the onset of cognitive symptoms,² the emphasis is on shifting toward markers that permit early detection and treatment.

Mild cognitive impairment (MCI) is a premorbid risk factor for dementia representing a transitional state with objective cognitive impairment but with functional independence maintained.³ However, the annual rate of progression to dementia ranges from only 8% in clinical trials⁴ to 13% in large registries.⁵ Furthermore, the objective cognitive impairment that defines MCI can be reversible, with rates of reversion to normal cognition (NC) as high as 16% within 1 year⁶ and additional reversions thereafter.⁷⁻⁹ Thus, the prognostic utility of MCI as an early marker of dementia may benefit from the incorporation of additional features to improve specificity.

Neuropsychiatric symptoms (NPS) in older adults are associated with cognitive decline in both NC and MCI populations.^{10,11} As with MCI, NPS alone can lack specificity depending on the natural history. When NPS are characterized by later-life onset, represent a distinct change from long-standing patterns of behavior and personality, are not better accounted for by a psychiatric disorder, and persist for >6 months, they define mild behavioral impairment (MBI).¹² These validated criteria, developed by an international consensus group under the rubric of the Alzheimer's Association, describe an important risk state for incident cognitive decline and dementia.¹² Moreover, MBI has been associated with Alzheimer disease (AD) risk genes, including the *APOE* ϵ 4 allele, *BINI1*, and *EPHA1*,¹³ as well as higher AD polygenic risk scores¹⁴ and markers for amyloid, tau, and neurodegeneration.¹⁵⁻²¹

One possibility is that incorporating NPS into case finding in populations without dementia may improve the specificity of MCI. Although MBI can be the index manifestation of dementia and precede mild cognitive changes,²²⁻²⁶ the co-occurrence of MCI and MBI may represent a unique state with a heightened risk of disease progression that is less likely to revert to normal cognitive function. Here, we examined participants with MCI, stratified by MBI status at baseline, and their cognitive status at 3 years. We hypothesized a higher likelihood of progression to dementia and a lower likelihood of reversion back to NC when MCI and MBI are comorbid.

Methods

Study Population: National Alzheimer's Coordinating Center

Data used in this study were obtained from the National Alzheimer's Coordinating Center (NACC) database.²⁷ NACC was established by the National Institute on Aging and consists of multiple National Institute on Aging–funded Alzheimer's Disease Research Centers (ADRCs) that recruit and collect data on participants with cognitive function ranging from normal to dementia. The ADRCs contribute to the NACC Uniform Data Set (UDS) using a prospective, standardized, and longitudinal clinical evaluation administered approximately annually. Sixteen data collection forms are completed by the clinician, covering demographics, neurologic examination findings, and diagnosis. Cognitive diagnosis from the clinician UDS D1 form was used for this study, which included coding for NC, MCI, and dementia, according to the relevant clinical criteria.²⁸⁻³⁰ Detailed information on the cohort and the UDS is described elsewhere.²⁸⁻³⁰ *APOE* genotype is reported by the Centers on the Neuropathology form and the Alzheimer's Disease Genetics Consortium and sent to NACC. The number of ϵ 4 alleles is reported as 0, 1, or 2 and was dichotomized to carrier status for these analyses. NACC-UDS with a November 2020 data freeze was used for this study.

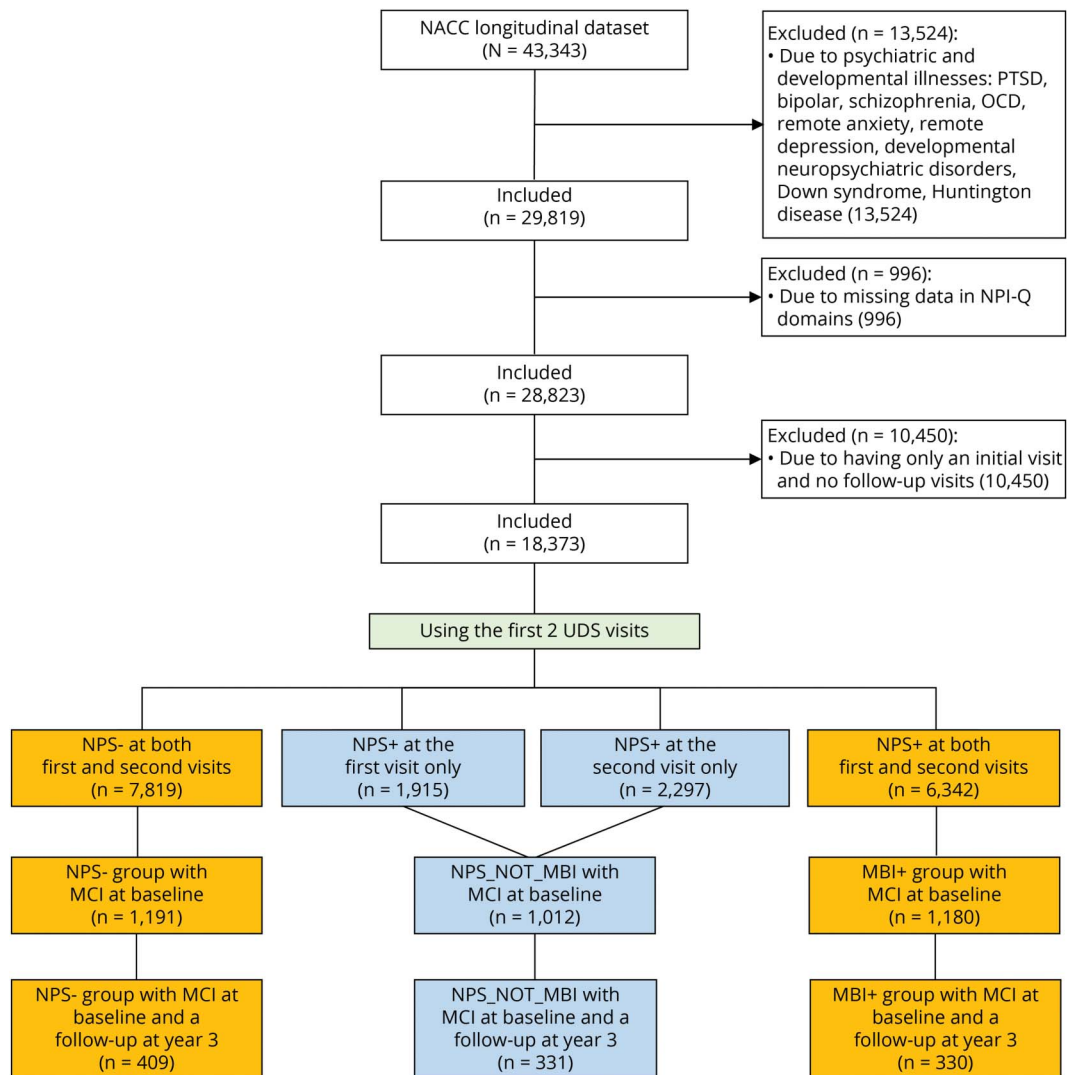
Standard Protocol Approvals, Registrations, and Patient Consents

As determined by the University of Washington Human Subjects Division, use of the NACC database itself is exempt from Institutional Review Board review. However, all contributing ADRCs are required to obtain informed consent from their participants and to maintain their own separate Institutional Review Board review and approval from their institution before submitting data to NACC.

Participant Selection

Participant selection is illustrated in Figure 1. NACC participants enrolled between 2005 and 2020 were included. Participants were eligible for this analysis if they were ≥ 60 years of age, had 2 consecutive visits after enrollment with valid NPI-Q data (to determine NPS and MBI), had follow-up data at 3 years, and had a diagnosis of MCI at the second study visit in accordance with the Petersen³¹ criteria. Eligible participants were excluded from the analyses if they had a prior diagnosis of a psychiatric condition, including bipolar disorder, depression,

Figure 1 Flowchart of Participants From NACC Included for Analysis



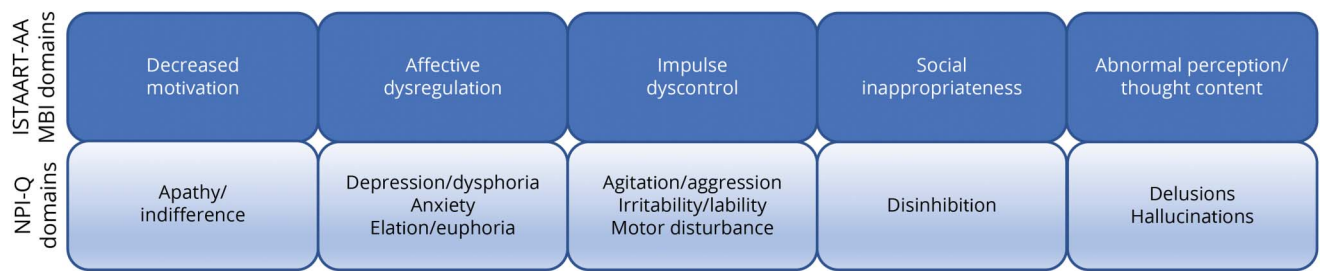
Primary sample is shown in amber, and NPS+ subsample retained for secondary analyses is shown in blue. MBI = mild behavioral impairment; MCI = mild cognitive impairment; NACC = National Alzheimer's Coordinating Center; OCD = obsessive compulsive disorder; NPS = neuropsychiatric symptoms; NPI-Q = Neuropsychiatric Inventory Questionnaire; PTSD = posttraumatic stress disorder; UDS = Uniform Data Set.

anxiety, obsessive compulsive disorder, posttraumatic stress disorder, or schizophrenia, because NPS in this context may not be of late onset and preclude MBI diagnosis. Developmental or neurologic conditions, including neuropsychiatric disorders and genetic conditions such as Down syndrome or Huntington disease, were also exclusion criteria.

MBI status was derived from the UDS using a published algorithm^{32,33} to transform the Neuropsychiatric Inventory Questionnaire (NPI-Q)³⁴ items to MBI domains. The NPI-Q is an informant-rated instrument with excellent test-retest validity³⁴ assessing the severity (absent, mild, moderate, and severe) and distress associated with 12 neuropsychiatric domains over the last month. Because the MBI criteria require later-life-emergent NPS to be persistent for ≥ 6 months, the NPI-Q cannot inform the persistence criterion without

repeated administration over an interval of at least 6 months or in the case of NACC in its annual assessments. Ten of the 12 domains assessed by the NPI-Q align with the 5 International Society to Advance Alzheimer's Research and Treatment-Alzheimer's Association (ISTAART-AA) domains of MBI (Figure 2), namely (1) decreased drive/motivation (apathy/indifference), (2) emotional dysregulation (depression/dysphoria, anxiety, elation/euphoria), (3) impulse dyscontrol (agitation/aggression, irritability/lability, aberrant motor behavior), (4) social inappropriateness (disinhibition), and (5) abnormal perception or thought content (delusions and hallucinations). To derive MBI domain scores, the NPI-Q severity ratings for each of its corresponding MBI domains were used to determine the presence of NPS per domain. The MBI criterion of symptom persistence was operationalized by requiring NPS to be endorsed at 2 consecutive NACC visits, the latter of

Figure 2 Schematic Overlap of the NPI-Q and ISTAART-AA MBI Domains



ISTAART-AA = International Society to Advance Alzheimer's Research and Treatment–Alzheimer's Association; MBI = mild behaviour impairment; NPI-Q = Neuropsychiatric Inventory Questionnaire.

which was determined as the neurobehavioral baseline (MBI+). MBI– participants had no positive scores. MBI scores were derived from the mean of the 2 consecutive NACC visits (range 0–30), with the cut point for MBI+ being a total score ≥ 0 .

This approach yielded a primary final sample of 409 participants with no past or current NPS (NPS–) and 330 participants who met the NPS emergence and persistence criteria for MBI (MBI+). In addition to these participants, a sample of 331 participants developed late-onset NPS at either the first or second NACC visit (NPS+) but did not meet the MBI persistence criteria because they did not have NPS at both. These individuals with NPS_NOT_MBI were retained for a separate secondary analysis.

Cognitive Status at Follow-up

We defined cognitive status at follow-up using NACC UDS clinician diagnosis at baseline and after 3 years of follow-up. We adopted a conservative definition of reversion to NC, namely a clinician diagnosis of NC after 3 years of follow-up, whereas Impaired-Not-MCI was retained with MCI as stable MCI. Progression to dementia was defined as a clinician diagnosis of dementia.

Statistical Analysis

The primary analysis involved the NPS– and MBI+ comparison, and secondary analyses involved the NPS_NOT_MBI (i.e., transient NPS) group.

Demographic characteristics were examined for NPS–, NPS_NOT_MBI, and MBI+ participants by χ^2 tests for categorical variables and 1-way analysis of variance for continuous variables.

The distribution of cognitive diagnoses at the 3-year follow-up point was assessed with χ^2 tests and the likelihood ratio. This distribution was further quantified with multinomial logistic regression adjusted for age, sex, race, years of education (continuous), and APOE $\epsilon 4$ carrier status to assess the progression to dementia or reversion to NC relative to stable MCI at the 3-year UDS visit. Event rates were annualized to determine progression and reversion rates.

Statistical analyses were performed in IBM SPSS Statistics version 26 (Armonk, NY). Statistical significance was set at $\alpha \leq 0.05$.

Data Availability

Data access was provided by NACC on the basis of an approved research proposal.

Results

The characteristics of our final sample are described in the Table. The primary sample involved $n = 409$ NPS– individuals and $n = 330$ MBI+ individuals. An intermediary group ($n = 331$) with no history of NPS presenting with late-onset NPS that did not meet MBI duration criteria was retained for secondary analyses (NPS_NOT_MBI). There were group differences in racial ($\chi^2 = 22.6, p = 0.012$) and sex ($\chi^2 = 34.4, p < 0.001$) distributions, and the MBI+ group was significantly younger ($F_{2, 1,067} = 8.7, p < 0.001$). There were no statistically significant differences in years of education, Mini-Mental State Examination (MMSE) score, or APOE $\epsilon 4$ carrier status.

In the primary sample of NPS– and MBI+ participants, 238 participants (33.6%) progressed to dementia, and 90 participants (12.2%) reverted to NC. The UDS definitions were paralleled in MMSE scores, with a diagnosis of dementia at 3 years associated with average scores of 21.5 ± 4.8 , stable MCI with average scores of 27.0 ± 2.9 , and reversion to NC with average scores of 28.6 ± 1.3 ($F_{2,720} = 213.2, p < 0.001$).

The NPS– and MBI+ groups differed in their likelihood of progressing to AD and reverting to NC ($\chi^2 = 34.7, p < 0.001$; Figure 3A). Multinomial logistic regression in which stable MCI was the reference with adjustment for age, sex, education (continuous), race, and APOE $\epsilon 4$ carrier status revealed that MBI+ participants were more likely than NPS– participants to progress to dementia (adjusted odds ratio [AOR] 2.10, 95% CI 1.47–2.99, $p < 0.001$) and less likely to revert to NC (AOR 0.45, 95% CI 0.26–0.80, $p < 0.01$). Annual progression rates to dementia were 14.7% for MBI+ participants and 8.3% for NPS– participants, while annual reversion rates were 2.5% for MBI+ participants and 5.3% for NPS– participants.

Table Demographic Characteristics of the Included Sample

	NPS–	NPS+	MBI+	χ^2 Test	F Value	p Value
No.	409	331	330	—	—	—
Age, mean (SD), y	76.0 (8.2)	76.5 (7.9)	74.0 (8.8)	—	8.77	<0.001
Sex, n (%)				34.40	—	<0.001
Male	206 (50.4)	179 (54.1)	125 (49.2)			
Female	203 (49.6)	152 (45.9)	129 (50.8)			
Education, mean (SD), y	15.4 (3.1)	15.6 (3.3)	15.6 (3.3)	—	0.60	0.548
Race, n (%)				22.60	—	0.012
White	309 (75.6)	268 (81.0)	284 (86.1)			
Black	80 (19.6)	43 (13.0)	48 (9.1)			
Asian	13 (3.2)	8 (4.2)	13 (3.9)			
Other	7 (1.7)	6 (1.8)	3 (0.9)			
MMSE score	27.3 (2.1)	27.0 (2.3)	26.8 (2.8)		2.97	0.052
APOE ϵ4 carrier, n	157 (41.6; valid n = 377)	135 (43.8; valid n = 308)	149 (48.1; valid n = 310)	2.88		0.23

Abbreviations: MBI = mild behavioral impairment; MMSE = Mini-Mental State Examination; NPS = neuropsychiatric symptoms.

We repeated analyses using a more liberal definition of reversion from MCI, in which Impaired-Not-MCI was also considered reversion. The number of participants who reverted with this definition increased to 135 (18.3%), and the MBI+ and NPS– groups once again differed in their likelihood of progressing to dementia and reverting to NC ($\chi^2 = 33.8$, $p < 0.001$). Multinomial logistic regression in which stable MCI was the reference with adjustment for age, sex, education (continuous), race, and APOE ϵ 4 carrier status revealed that MBI+ participants were more likely than NPS– participants to progress to dementia (AOR 2.06, 95% CI 1.43–2.96, $p < 0.001$) and less likely to revert to NC (AOR 0.58, 95% CI 0.36–0.92, $p < 0.05$).

As a secondary analysis, we examined outcomes in participants with MCI without NPS and the independent group of participants with NPS but for whom symptoms were present for <6 months who therefore did not meet the MBI persistence criterion (NPS_NOT_MBI). After 3 years, 142 participants (42.9%) progressed to dementia, and 52 participants (15.7%) had reverted to NC. This distribution did not differ from those with NPS_NOT_MBI at the first or second visit ($\chi^2 = 0.88$, $p = 0.64$) or from the MBI+ group ($\chi^2 = 1.20$, $p = 0.54$); however, they significantly differed from the NPS– group ($\chi^2 = 27.12$, $p < 0.001$; Figure 3B). Multinomial logistic regressions were repeated in which stable MCI was the reference with adjustment for potential confounders, which revealed that NPS_NOT_MBI participants were more likely than NPS– participants to progress to dementia (AOR 2.25, 95% CI 1.59–3.19, $p < 0.001$) but not less likely to revert to NC (AOR 0.92, 95% CI 0.57–1.48, $p = 0.74$). The annual rate of progression to dementia was 14.3% for the late-onset NPS_NOT_MBI participants.

Cognitive testing confirmed the increased risk of cognitive decline with the co-occurrence of MCI and MBI (Figure 3C). After 3 years, participants with MBI+ and NPS_NOT_MBI had significantly lower MMSE scores than NPS– participants.

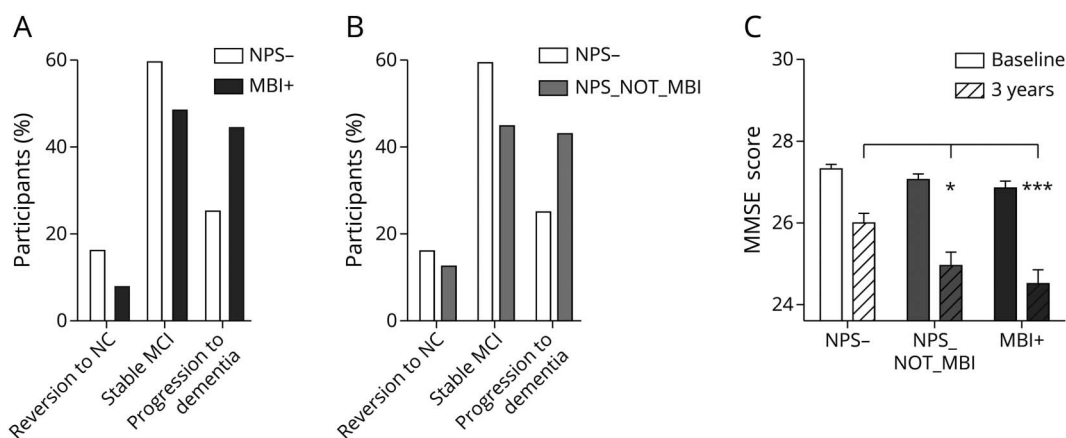
Discussion

Our longitudinal analyses demonstrate that MBI and late-life-onset NPS improve the specificity of MCI as an at-risk state for incident dementia. Although increased risk for dementia has previously been associated with NPS, this study demonstrates that MCI comorbid with MBI is associated with a lower rate of reversion to NC. Specifically, individuals with comorbid MCI and MBI are at 2-fold greater risk for progression to dementia over 3 years and less than half as likely to revert to NC compared to individuals with MCI but no NPS. Our findings have important clinical implications and indicate that both cognitive function and NPS should be assessed as a matter of routine to improve prognostication.

The importance of MCI conceptually and as a clinical entity cannot be understated. Through identification of premorbid individuals at risk for dementia using a combination of objective cognitive performance and function,³ patients can be identified for early intervention. However, specificity is suboptimal; many individuals with MCI do not progress to dementia, and despite objective signs of cognitive impairment, some individuals revert to a state of NC.

A meta-analysis assessed the progression rate from MCI to dementia across 41 cohort studies stratified by population studies and clinical trials.⁴ A cumulative proportion of 28.9%

Figure 3 Progression to AD or Stable MCI and Reversion to NC After 3 Years



AD = Alzheimer disease; MBI = mild behavioral impairment; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NC = normal cognition; NPS = neuropsychiatric symptoms.

and 33.6% of individuals with MCI progressed to AD in population studies and clinical trials, respectively.⁴ More than half of the participants did not progress to dementia at 10 years with an annual progression rate of $\approx 7\%$ (AD progression rate 6.8% in population studies and 8.1% in clinical trials). In clinical settings, the rate of progression is higher, estimated at 13.7% person-years (95% CI 13.5%–13.9%).⁵ The annual progression rate observed in our sample of participants with MCI without NPS therefore aligns with population data, whereas comorbid MCI and MBI, or MCI and late-onset NPS, had a more malignant course.

The reversion from MCI to NC has received less attention than progression to dementia.³⁵ One meta-analysis looking at reversion rates across 25 studies found that 8% of participants in population studies and 25% in the clinical setting reverted from MCI to NC.⁹ Another longitudinal study of 473 individuals with MCI tracked reversion rates to NC in a community-based cohort and found that 44% of the cohort reverted to NC over a 6-year follow-up.³⁶ Very similar results were recently reported in a community follow-up study wherein 752 individuals with incident MCI were followed up for a mean of 2.4 years, over which time 47% no longer met MCI criteria.³⁷

Several studies in participants with MCI have demonstrated that the presence of NPS, assessed with the NPI-Q, is associated with a greater risk of progression to dementia.^{38–40} Even subtle NPS in individuals with MCI have been associated with cognitive decline.⁴¹ Similarly, a machine learning study compared NPS in 128 participants (78 with NC, 50 with MCI) and progression to dementia. NPS proxies such as the NPI-Q total severity and stress scores were the most important factors predicting progression to dementia from MCI, and the authors concluded that NPS were associated with a higher risk for dementia in MCI.⁴²

Mixed findings have emerged when examining the relationship between NPS and reversion from MCI to NC.^{43,44}

Specifically, a population-based longitudinal study of 622 participants with MCI with 6- and 12-year follow-up analyses⁴⁴ determined that depression, assessed with the Comprehensive Psychiatric Rating Scale,⁴⁵ did not explain reversion to NC. Complicating the interpretation of this analysis, however, was an unusually low prevalence of depression⁴⁶ and a very high reversion rate of 58%. Conversely, in a subanalysis from the NACC cohort, the stability of MCI was examined in 1,121 participants who had previously been determined to have NC and then developed MCI. This study reported that 28.9% of the sample reverted to NC over a mean follow-up of 5.5 years and that reversion to NC was associated with lower burden of mood, anxiety, and hyperactivity symptoms, as well as the initiation of cognitive medications.⁴⁴ Our findings may reconcile these conflicting findings, indicating that late-onset NPS are enriched in an emergent MCI sample and conversely that low rates of NPS are associated with a greater likelihood of reversion from MCI to NC.

The prognostic utility of MBI arises from 2 criteria: symptoms are later life emergent, and symptoms are persistent. The former distinguishes MBI from psychiatric illness, and the latter eliminates transient symptoms that may manifest in response to life events. These criteria increase the signal-to-noise ratio for identification of behavioral symptoms that represent sequelae of neurodegeneration. Consistent with this, a recent longitudinal study of 2,769 individuals with NC reported that 51.6% of those with MBI demonstrated cognitive and functional decline over 3 years compared to 21.7% of the MBI- group.²⁴ Similarly, a machine learning study of Alzheimer's Disease Neuroimaging Initiative participants determined that later-life-emergent and persistent NPS (i.e., MBI) and hippocampal atrophy were the features that best predicted dementia diagnosis 40 months hence, with comparable magnitudes of effect.⁴⁷ Thus, converging data indicate that MBI improves clinical prognostication for cognitive decline and dementia in the older adult population.

To derive MBI status from NACC data, we transformed 2 visits of the NPI-Q data into MBI scores.³² While our data transformation approach has been used in prior studies, the NPI-Q was designed for a dementia population,^{38,42,48} and we did not use convergent measures to validate the presence of NPS when identified by informants with the NPI-Q. Furthermore, while the NPI-Q has very good psychometric properties, the instrument is completed by informants and therefore is subject to certain limitations, including the informant's neuropsychiatric state, cognitive function, recall bias, and cultural beliefs, among others. Future studies should consider the MBI checklist,⁴⁹⁻⁵¹ which captures later-life onset of persistent and impactful NPS in accordance with the ISTAART-AA MBI criteria and which was developed specifically for populations without dementia as in this study. The MBI-C can be completed by self or informant. Because we restricted our hypothesis to individuals with MCI, our analyses do not determine whether MBI in NC is associated with greater risk. Recently published data from an NACC sample have determined the 3-year risk for incident MCI/dementia in NC. The 3-year progression rate from NC to dementia was higher in MBI+ (2.3%) vs MBI- (0.2%) individuals.²⁴ However, this is substantially lower than the 3-year progression rates to dementia in MBI+ MCI+ (44.1%) and MCI+ NPS- (24.9%) individuals. Together, these findings indicate that MBI and MCI are not simply additive and may have synergistic effects on the risk of progression to dementia.

Integrating NPS characterizations into dementia risk assessment improves the specificity of MCI as an at-risk state for dementia. When comorbid with MBI, MCI is associated with a greater risk of progression to dementia and a significantly reduced likelihood of reverting to NC. This has implications for prognostication in clinical practice and may be a means of identifying high-risk premorbid individuals for biomarker and treatment studies.

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