Prevalence, Clinical Correlates, Cognitive Trajectories, and Dementia Risk Associated With Mild Behavioral Impairment in Asians

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ABSTRACT

Objective: Mild behavioral impairment (MBI) is characterized as later-life–emergent and persistent neuropsychiatric symptoms (NPS). The symptom persistence criterion of MBI has shown to increase the signal-to-noise ratio of the syndrome, decreasing the likelihood of false-positive NPS. However, the long-term cognitive and prognostic impact of MBI remains to be evaluated against the traditional framework of NPS, especially in Asian cohorts. This study investigated the epidemiologic characteristics of MBI in a prospective clinical cohort of Singaporean elderly.

Methods: A total of 304 dementia-free individuals (mean [SD] age = 72.2 [8.0] years, 51.6% female) were recruited between August 2010 and October 2019. All participants underwent annual neuropsychological, neuropsychiatric, and clinical assessments for 4 consecutive years and were diagnosed as having no cognitive impairment (NCI) or cognitive impairment–no dementia (CIND). MBI was ascertained using both baseline and year-1 Neuropsychiatric Inventory assessments. Cognitive *Z*-scores and Clinical Dementia Rating Sum-of-Boxes (CDR-SoB) scores were calculated.

Results: The prevalence of MBI was 14.5% (7.1% of NCI, 12.9% of CIND-mild, and 24.7% of CIND-moderate patients). MBI patients showed poorer cognitive function at baseline ($F_{1,295} = 8.13$ [SE = 0.47], $P = .005$), primarily in memory and executive function domains. MBI was associated with accelerated decline in global cognition (β = –0.15; 95% CI, –0.23 to –0.07) along with faster increase in CDR-SoB (β = 0.92; 95% CI, 0.62 to 1.21) as compared to individuals without symptoms or transient NPS. A total of 38.6% of MBI patients developed dementia as compared to 12.3% of non-MBI elderly ($\chi^2 = 19.29$, $P < .001$). MBI increased risk of incident dementia by 2.56-fold as compared to no symptoms or transient NPS, regardless of cognitive impairment.

Conclusions: MBI is a neurobehavioral risk factor for dementia, representing a potential target for dementia risk modeling, preventive intervention, and disease management.

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Neuropsychiatric symptoms (NPS) are a common behavioral and psychological feature of dementia associated with greater caregiver burden and cognitive impairment.[1,2] While some NPS such as post-stroke mood disturbances are transient,[3] many can be persistent.[4,5] Alzheimer's disease (AD) patients showing persistent NPS tended to have greater cognitive and functional decline as compared to patients with no or fluctuating symptoms.[6] The diagnostic construct of mild behavioral impairment (MBI) has been proposed to identify an at-risk group for dementia. MBI is characterized by later-life–emergent and persistent behavioral, perception, or personality changes in non-demented individuals.[7] The symptom persistence criterion of MBI has proven to be a robust feature, increasing the signal-to-noise ratio of the syndrome and decreasing the likelihood of false-positive NPS.[8–10]

MBI was reported in 14.5%–32% of dementia-free elderly in a recent systematic review[11] of studies, although with several different MBI case definitions. MBI patients, with or without concurrent cognitive impairment, showed poorer cognitive performance, particularly in the memory and executive function domains.[12] It was also found that elderly with MBI showed a faster short-term (1-year) cognitive decline as compared to individuals with MBI symptom severity below threshold.[13] The rates of conversion to dementia were also higher in MBI patients (29%–71%)[9,14,15] relative to individuals with NPS viewed in a more traditional framework (5%–50%) when only symptoms in the previous month were captured.[16–18]

However, most previous studies have been done in Western populations, with a limited number in Asian cohorts that had relatively smaller sample sizes and shorter follow-up periods.[11] A number of previous studies included neurology and psychiatric outpatients[14,15] or patients with mild cognitive impairment (MCI),[12,19] which is a heterogeneous group with a broad spectrum of cognitive severity. Further evaluation is warranted on the long-term effects of MBI across groups with varying dementia conversion risks. Furthermore, as most existing studies have captured short-term (1–6 months) NPS,[11] it is optimal to have repeated assessments to confirm

Clinical Points

- Mild behavioral impairment (MBI) is a risk factor for dementia, but it is unclear if MBI confers a greater risk of cognitive decline and dementia beyond transient neuropsychiatric symptoms (NPS), especially among Asian elderly.
- Incorporating MBI evaluations into clinical assessments can lead to better risk modeling and identification of patients who are at heightened risk of cognitive decline and in need of timely intervention.

the persistence of NPS and prevent false-positives due to transitory symptoms or reactive states.[20] Therefore, it remains crucial to examine the prevalence of MBI and evaluate its impact on long-term cognitive and clinical outcomes, which will aid the understanding and identification of MBI as a potential early manifestation of neurocognitive disorders.

Here, we investigated the prevalence of MBI using established criteria[7] and examined the clinical and cognitive correlates of MBI in a cohort of dementia-free memory clinic participants with a spectrum of cognitive impairment. We further evaluated the impact of MBI on cognitive trajectory and clinical prognosis for up to 4 years and in comparison to individuals with transient NPS (single occurrence of symptoms). We hypothesized that MBI predicts faster cognitive and functional decline and a greater risk of incident dementia as compared to transient NPS.

METHODS

Study Participants

This study was conducted as part of an ongoing prospective cohort study that recruits individuals from memory clinics and the community in Singapore. Participants were aged ≥ 50 years, had sufficient language skills for neuropsychological assessments, and fulfilled diagnostic criteria of (*a*) no cognitive impairment (NCI)—no objective cognitive impairment on a comprehensive neuropsychological test battery[21] or functional loss—or (*b*) cognitive impairment–no dementia (CIND)—impaired in ≥ 1 cognitive domain on the neuropsychological test battery without loss of daily functions. Cognitive impairment in each test of each domain was defined as ≥ 1.5 standard deviations (SDs) below education-adjusted norms, and impairment in at least half of the tests in each domain was characterized as impairment in that domain. Exclusion criteria of this study were major psychiatric illness or substance abuse disorder (*DSM-IV*), cognitive impairment caused by a history of traumatic brain injury, multiple sclerosis, tumor, epilepsy or systemic disease, significant visual and auditory abnormalities, and diagnosis of dementia according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), criteria.

A total of 342 dementia-free participants who had completed at least 1 follow-up visit were enrolled in the study between August 2010 and October 2019. All participants were invited to undergo annual clinical, neuropsychological, physical, and laboratory examinations at the National University Hospital and biennial magnetic resonance imaging (MRI) brain scans for up to 5 years. Thirty-eight participants without NPS data for MBI diagnosis were excluded, leaving a total of 304 participants for the current analysis. For neurocognitive trajectory analysis, 177 participants had neuropsychological data available at all follow-up visits while 127 had data from at least 1 follow-up visit available (72 had data from 3, 18 had data from 2, and 37 had data from 1 visit). Ethics approval for this study was obtained from the National Healthcare Group Domain-Specific Review Board. Written informed consent was obtained in the preferred language of the participants prior to recruitment. The study was conducted in accordance with the Declaration of Helsinki.

MBI Assessment

We assessed MBI according to the International Society to Advance Alzheimer's Research and Treatment of the Alzheimer's Association (ISTAART-AA) criteria[7] using the Neuropsychiatric Inventory (NPI).[22] MBI was classified based on having NPS consecutively at baseline and year 1. Nine participants had no NPI data at baseline, and hence their NPI data at year 1 and year 2 were used to determine the presence of MBI. We operationalized 10 NPI items for the 5 MBI domains of decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception/thought content following a previously validated algorithm.[10,23] The persistent presence of at least 1 symptom within the respective domain was classified as the presence of that MBI domain. Non-MBI participants were further identified as having no symptoms, transient NPS (NPS at baseline only), or incident NPS (NPS at year 1 but not at baseline).

Research Diagnosis

Diagnoses were determined at weekly consensus meetings among clinicians, neuropsychologists, radiologists, and research personnel during which details of the clinical investigations, neuropsychological assessments, and brain scans were reviewed. At baseline, participants were diagnosed as having NCI (n = 99), CIND-mild (≤ 2 impaired domains on neuropsychological test battery; n = 116), or CIND-moderate (>2 impaired domains on neuropsychological test battery; n = 89). At follow-up assessments, dementia was diagnosed according to the *DSM-IV* criteria. We also conducted annual clinical interviews using the Clinical Dementia Rating (CDR) scale,[24] and the CDR Sum-of-Boxes (CDR-SoB) scores were used to determine functional decline.

Neuropsychological Assessments

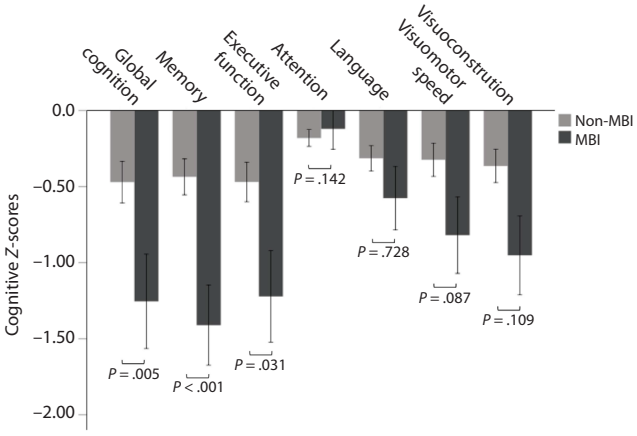
Participants underwent annual Mini-Mental State Examination (MMSE)[25] assessment and a comprehensive neuropsychological test battery (the National Institute of Neurologic Disorders and Stroke and Canadian Stroke Network protocol) comprising the cognitive domains of attention/working memory (Digit span forward and

Table 1. Baseline Participant Characteristics[a]

Characteristic	Non-MBI, n = 260 (85.5%)	MBI, n = 44 (14.5%)	*P*
Demographics			
Age, mean (SD), y	71.4 (7.7)	73.0 (8.2)	.200
Sex (female), n (%)	137 (52.7)	20 (45.5)	.374
Ethnicity (Chinese), n (%)	224 (86.2)	38 (86.4)	.970
Education, mean (SD), y	8.1 (4.8)	8.1 (5.6)	.977
Diagnosis, n (%)			**.002**
NCI	92 (35.4)	7 (15.9)	
CIND-mild	101 (38.8)	15 (34.1)	
CIND-moderate	67 (25.8)	22 (50.0)	
APOE-ε4 carrier, n (%)	67 (25.8)	11 (25.0)	.914
Vascular Risk Factors, n (%)			
Hypertension	176 (67.7)	31 (70.5)	.716
Hyperlipidemia	197 (75.8)	33 (75.0)	.912
Diabetes mellitus	77 (29.6)	20 (45.5)	**.037**
History of stroke	62 (23.8)	13 (29.5)	.417
History of heart disease	15 (5.8)	1 (2.3)	.337
Current smoker	23 (8.8)	3 (6.8)	.656
Neuropsychological Measures			
MMSE score, mean (SD)	25.2 (3.3)	23.5 (3.6)	**.001**
CDR-SoB score, median (range)	0 (0–4.0)	1.0 (0–3.5)	**.002**

[a]Boldface indicates statistical significance.
Abbreviations: APOE-ε4 = apolipoprotein E ε4 allele, CDR-SoB = Clinical Dementia Rating Sum-of-Boxes, CIND = cognitive impairment–no dementia, MBI = mild behavioral impairment, MMSE = Mini-Mental State Examination, NCI = no cognitive impairment.

Figure 1. Cross-Sectional Differences in Global and Domain-Specific Cognitive *Z*-Scores Between MBI and Non-MBI Individuals[a]



[a]General linear models with Bonferroni correction for multiple comparisons, adjusted for age, sex, education, diabetes mellitus, diagnosis, and year of MBI status. Ranges shown are 95% CIs.
Abbreviation: MBI = mild behavioral impairment.

backward), memory (Rey-Osterrieth Complex Figure Test [RCFT]—immediate and delayed recall and recognition, Hopkins Verbal Learning Test immediate and delayed recall and recognition), executive function (Color Trails Test 1 and 2, Animal Fluency test), language (Modified Boston Naming Test), visuomotor speed (Symbol-Digit Modalities Test), and visuoconstruction (RCFT-copy).[26,27] Raw scores of each test in the comprehensive test battery were standardized using the means and SDs of the reference group (NCI or CIND-mild without MBI) to compute *Z*-scores, which were averaged and standardized for each cognitive domain. Domain-specific *Z*-scores were averaged and standardized to derive a global composite *Z*-score indicative of global cognitive function.

Vascular Risk Factors and Clinical Measures

Vascular risk profile was obtained through clinical interview, physical examination, and review of laboratory and medical records. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive medication. Diabetes mellitus was defined as glycated hemoglobin ≥ 6.5% or use of diabetic medication. Hyperlipidemia was defined as total cholesterol levels ≥ 4.14 mmol/L or use of lipid-lowering medication. Heart disease was defined as presence of coronary artery disease, ischemic heart disease, or atrial fibrillation. Stroke was defined as having a clinical history of rapid-onset focal or global neurologic deficits for > 24 hours and confirmed on medical records. Apolipoprotein E (APOE) genotyping was performed following standardized procedures,[28] and APOE ε4 allele (APOE-ε4) carrier positivity was determined by the presence of at least one ε4 allele.

Statistical Analysis

First, unadjusted group differences between MBI and non-MBI participants in demographics, risk factors, and clinical and cognitive measures were tested using χ^2 tests for categorical variables and independent-sample *t* tests/Mann-Whitney *U* tests for continuous variables. Next, we conducted general linear models analyses to compare global and domain-specific cognitive *Z*-scores at baseline between MBI and non-MBI participants, adjusting for age, sex, education, diagnosis, year of MBI diagnosis (year 1/year 2), and risk factors that were statistically significant in the group comparison.

Second, we conducted linear mixed models (LMM) analyses using an unstructured covariance matrix to compare the rates of change in cognitive *Z*-scores and CDR scores over 4 years. For each model, the presence of MBI, time, and their interaction were entered as fixed factors; age, sex, education, baseline diagnosis, year of MBI diagnosis, and risk factors that were statistically significant in the group comparison as covariates; and global cognitive *Z*-scores and CDR-SoB scores as dependent variables. To compare the effects of MBI on rates of change in cognitive *Z*-scores and CDR-SoB scores at different levels of cognitive burden, we added the interaction between MBI, cognitive burden (CIND-moderate vs NCI/CIND-mild), and time as a fixed factor in LMM. NCI and CIND-mild participants were previously found to have similar cognitive trajectory and MRI findings.[29,30]

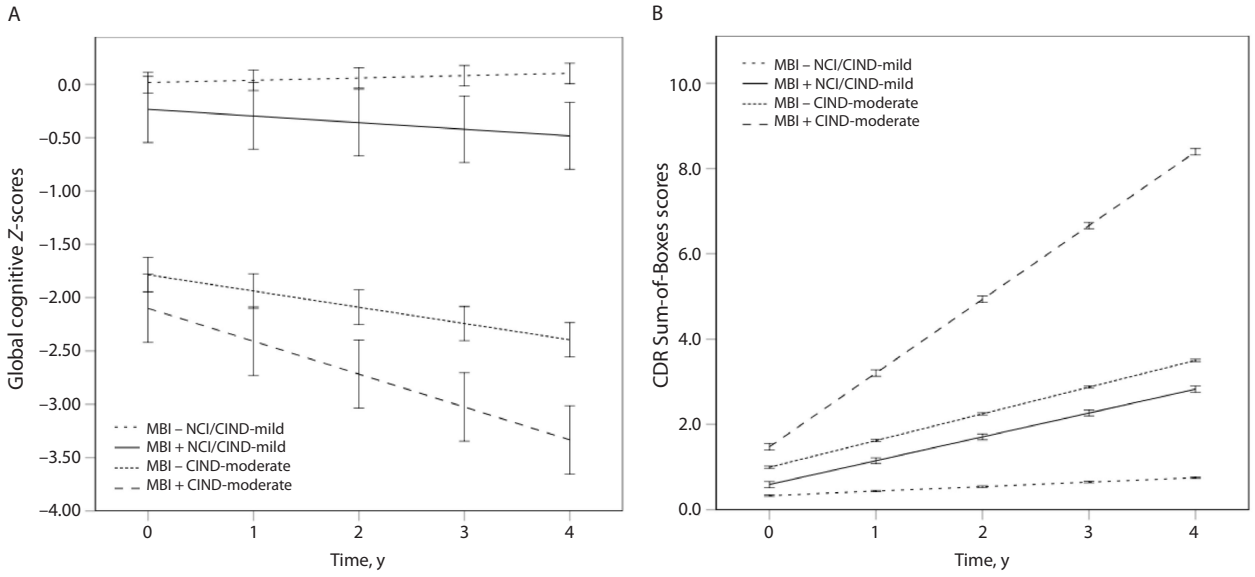
Third, we used Kaplan-Meier curves for survival analysis and Cox proportional hazards models to evaluate the effect of MBI and its interaction with cognitive burden on the development of dementia over 4 years, adjusting for age, sex, year of MBI diagnosis, and baseline diagnosis. All analyses were performed using IBM SPSS Statistics 26 (2019).

Table 2. Effects of MBI on Cognitive Performance, CDR-SoB, and Risk of Incident Dementia[a]

	Change in Global Cognitive *Z*-Scores[b]		Change in CDR-SoB Scores[b]		Incident Dementia[c]	
Variable	β	95% CI	β	95% CI	HR	95% CI
Compared to no symptoms						
Transient NPS	**–0.06**	**-0.13 to –0.01**	0.20	–0.03 to 0.43	1.64	0.68 to 3.95
MBI	**–0.20**	**-0.27 to –0.12**	**1.03**	**0.76 to 1.31**	**4.35**	**1.89 to 9.98**
Compared to transient NPS						
MBI	**–0.12**	**-0.23 to –0.02**	**0.73**	**0.27 to 1.18**	**2.53**	**1.14 to 5.65**

[a]28 participants with incident NPS were excluded from these analyses. Boldface indicates statistical significance.
[b]Adjusted for age, sex, education, diabetes, baseline diagnosis, and year of MBI status.
[c]Adjusted for age, sex, baseline diagnosis, and year of MBI status.
Abbreviations: CDR-SoB = Clinical Dementia Rating Sum-of-Boxes, HR = hazard ratio, MBI = mild behavioral impairment, NPS = neuropsychiatric symptoms.

Figure 2. Slopes of (A) Global Cognitive *Z*-Scores and (B) CDR-SoB scores as a Function of MBI and Cognitive Burden[a]



[a]Ranges shown are 95% CIs.
Abbreviations: CDR-SoB = Clinical Dementia Rating Sum-of-Boxes, CIND = cognitive impairment–no dementia, MBI = mild behavioral impairment, NCI = no cognitive impairment.

RESULTS

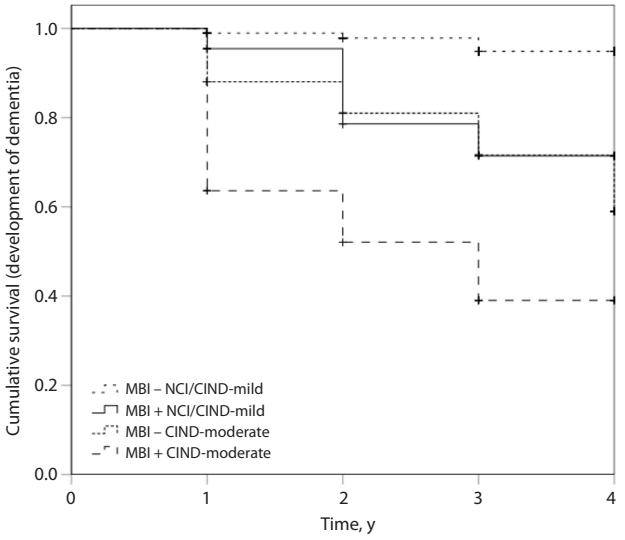
Prevalence and Characteristics of MBI

Of the 304 participants recruited (mean [SD] age = 72.2 [8.0] years, 51.6% female), we identified 14.5% (n = 44) with MBI and 85.5% (n = 260) as non-MBI (169 with no symptoms, 63 with transient NPS, 28 with incident NPS). MBI was identified in 7 NCI (7.1%), 15 CIND-mild (12.9%), and 22 CIND-moderate participants (24.7%). As summarized in Table 1, group comparisons showed that MBI participants had a higher rate of diabetes, lower MMSE scores, and higher CDR-SoB scores at baseline. The most frequent MBI domain was impulse dyscontrol (34.1%, n = 15), followed by affective dysregulation (11.4%, n = 5), decreased motivation (11.4%, n = 5), abnormal perception (11.4%, n = 5), and social inappropriateness (2.3%, n = 1).

Cognitive Profile of MBI

Baseline global cognitive performance differed significantly as a function of MBI ($F_{1,295} = 8.13$ [SE = 0.47], $P = .005$). MBI participants performed significantly poorer in the domains of memory ($F_{1,295} = 20.73$ [SE = 0.57], $P < .001$) and executive function ($F_{1,295} = 4.70$ [SE = 0.61], $P = .031$), but not attention, language, visuoconstruction, or visuomotor speed, even after Bonferroni correction for multiple comparisons (Figure 1). In the NCI/CIND-mild group, MBI participants performed significantly more poorly in memory ($F_{1,207} = 12.68$ [SE = 0.71], $P < .001$). In the CIND-moderate group, MBI participants performed worse in multiple domains including memory ($F_{1,82} = 7.61$ [SE = 0.55], $P = .007$), executive function ($F_{1,82} = 11.01$ [SE = 0.61], $P = .001$), visuoconstruction ($F_{1,82} = 4.04$ [SE = 1.63], $P = .048$), and visuomotor speed ($F_{1,82} = 10.30$ [SE = 0.28], $P = .002$).

Figure 3. Kaplan-Meier Survival Analysis for Incident Dementia as a Function of MBI and Cognitive Burden



Abbreviations: CIND = cognitive impairment–no dementia, MBI = mild behavioral impairment, NCI = no cognitive impairment.

Cognitive Trajectory of MBI

The significant interaction between MBI and time on global cognitive *Z*-scores indicated that MBI participants showed more rapid decline in global cognition relative to those without symptoms or with transient NPS (Table 2). Overall, MBI was associated with accelerated decline in global cognition (β = −0.15; 95% CI, −0.23 to −0.07) as compared to individuals without symptoms or transient NPS. Simple slope analyses showed that MBI participants declined (β = −0.11; 95% CI, −0.20 to −0.03; *P* = .007), while non-MBI participants (ie, those with no NPS or transient NPS) remained stable (β = 0.02; 95% CI, −0.05 to 0.01; *P* = .129) over 4 years. Specifically, MBI participants declined more rapidly in memory (β = −0.11; 95% CI, −0.19 to −0.04; *P* = .003), attention (β = −0.14; 95% CI, −0.22 to −0.06; *P* < .001), and language (β = −0.22; 95% CI, −0.37 to −0.07; *P* = .004) even after correction for multiple comparisons. The interaction between MBI, time, and cognitive burden showed that MBI was significantly associated with more rapid cognitive decline in the CIND-moderate group (β = −0.16; 95% CI, −0.27 to −0.04; *P* = .008) but not in the NCI/CIND-mild group (β = −0.08; 95% CI, −0.19 to 0.02; *P* = .120) (Figure 2A).

Functional Decline and Clinical Prognosis of MBI

The significant interaction between MBI and time on CDR-SoB scores showed that MBI participants had more rapid increase in CDR-SoB scores as compared to those without symptoms or with transient NPS (Table 2). Overall, MBI was associated with faster increase in CDR-SoB (β = 0.92; 95% CI, 0.62 to 1.21) as compared to non-MBI. This corresponded to a 2.93-point (95% CI, 1.86 to 4.00; *P* < .001) increase in the MBI group compared to a 0.54-point (95% CI, 0.36 to 0.72; *P* < .001) increase in the non-MBI group over 4 years. The interaction between MBI, time, and cognitive burden showed that MBI was significantly associated with faster CDR-SoB increase in both the CIND-moderate group (β = 1.10; 95% CI, 0.69 to 1.52; *P* < .001) and the NCI/CIND-mild group (β = 0.45; 95% CI, 0.07 to 0.84; *P* = .020) (Figure 2B).

Over 4 years, 38.6% (n = 17) of MBI patients developed dementia as compared to 12.3% (n = 32) of non-MBI elderly (24 with transient NPS and 8 without symptoms) ($\chi^2 = 19.29$, *P* < .001). MBI participants showed a significantly greater risk of incident dementia as compared to those without symptoms or with transient NPS (Table 2). Overall, MBI increased risk of incident dementia by 2.56-fold as compared to non-MBI, regardless of cognitive impairment. The significant interaction between MBI and cognitive burden showed that MBI was associated with a greater probability of incident dementia in both the CIND-moderate group (n = 35; hazard ratio [HR] = 2.06; 95% CI, 1.00 to 4.23; *P* = .05) and the NCI/CIND-mild group (n = 14; HR = 2.02; 95% CI, 2.02 to 21.76; *P* = .002) (Figure 3).

Sensitivity Analysis

The overall rate of data loss was 12.8%. We imputed missing longitudinal data for global *Z*-scores and CDR-SoB scores using the linear interpolation method.[31] We found that the effect of MBI remained significant on changes in global *Z*-scores (β = −0.13; 95% CI, −0.22 to −0.03; *P* = .007) and CDR-SoB (β = 0.36; 95% CI, 0.22 to 0.50; *P* < .001), suggesting the robustness of our results.

DISCUSSION

In this study of a non-demented Singaporean cohort with a wide spectrum of cognitive impairment, MBI was associated with (1) greater multidomain cognitive impairment at baseline; (2) accelerated cognitive and functional decline, indicated by faster rates of decline in the global cognitive scores and increase in CDR-SoB scores; and (3) an overall 2.6-fold increased risk of incident dementia over 4 years. These results support the notion that persistent later-life NPS may be an important neurobehavioral marker of cognitive decline leading to dementia.

In this study, we operationalized the requirement of 2 positive NPS assessments for MBI case ascertainment to capture individuals with persistent NPS, as emphasized in the MBI framework. We found an MBI prevalence of 14.5%, which is lower than those reported in previous MBI studies assessing 1-month NPS,[11] as there was more noise when transient NPS were included in the measure of risk. We found that individuals with MBI had a significantly higher rate of diabetes mellitus but not of other vascular risk factors. It was previously found that type 2 diabetes mellitus was related to the presence and incidence of NPS in MCI and early AD,[32,33] suggesting that diabetes may increase the susceptibility to psychopathological changes in cognitively impaired individuals. This treatable and preventable risk factor may therefore be a potential target in preventing the development of MBI, but would benefit from replication in further studies.

While the MBI domain of impulse dyscontrol was substantially higher among others in this Asian cohort, affective dysregulation was most common in a number of Western populations.[12,23] This may possibly be explained by some cultural differences, as it was found that American caregivers tend to have more depression-related and apathy-related distress than Asian caregivers, suggesting that Asians, who traditionally emphasized peace and moderation in the family, may be less sensitive to affective symptoms but more to hyperactive behaviors.[34] It was recently found that impulse dyscontrol symptoms appeared as the strongest neuropsychiatric condition for progression to dementia.[8,35] This finding could potentially be mediated by AD structural changes, including impaired white matter integrity and gray matter atrophy.[36] Hence, future studies with larger sample sizes could further evaluate if impulse dyscontrol and other MBI domains confer differential long-term impact on cognitive deterioration and disease progression.

We found that MBI is associated with poorer global cognitive function, driven by the domains of memory and executive function. Previous studies have also reported significantly worse performance in tests of working memory,[13] executive function, attention, and episodic memory in individuals with MBI regardless of cognitive status.[12] With a comprehensive neuropsychological battery and a longer follow-up duration, we are able to support the cognitive phenotype of MBI that was previously established but also extend these findings by evaluating the domain-specific cognitive trajectory of MBI. We found that participants with MBI had an accelerated decline in global cognition, particularly in the domains of memory, attention, and language, consistent with a previous study[13] showing a faster rate of decline in attention and working memory over 1 year. In addition to previous findings, we found that the impact of MBI on objective cognitive decline was significant only in individuals with moderate cognitive impairment. The cognitive impact of MBI in individuals with no or mild impairment did not reach statistical significance, which may be explained by higher mean (SD) years of education (8.7 [4.8] vs 6.7 [5.0] years) and younger age (70.0 [7.7] vs 75.3 [6.7] years) in this group. Alternatively, the study duration of 4 years may be insufficient to see change in this cognitively normal group. It is also possible that this group of elderly may show a more progressive decline in objective cognitive performance that may span over decades.[37]

However, we observed that MBI predicts accelerated functional decline and incident dementia across the spectrum of cognitive impairment. We found an overall 2.6-fold increased risk of dementia associated with MBI compared to non-MBI, including a 4.4-fold increase compared to participants without NPS and a 2.5-fold increase compared to participants with transient NPS, highlighting the dissociation between transient NPS and MBI. Therefore, identifying individuals with MBI may be a novel strategy for disease prevention or mitigation. Such identification could potentially be done by incorporating MBI evaluations into clinical assessments for better risk modeling and identifying patients who may require more timely intervention or benefit from clinical trials. Emerging evidence has suggested a link between MBI and AD pathology such as β-amyloid positron emission tomography (PET) burden,[38] plasma β-amyloid burden,[39] tau-PET and cerebrospinal (CSF) tau,[40] and plasma neurofilament light accumulation.[41] Further, recent evidence has also linked MBI and atrophy in the entorhinal cortex and hippocampus in a non-dementia sample of memory clinic patients.[42] Worsening of NPS was also found to be associated with small vessel disease progression.[43] Moving forward, more research should evaluate the neurobiological phenotype associated with MBI to establish whether MBI is a potential proxy for neurodegeneration or vascular changes.

This study has several limitations. First, we were not able to evaluate the impact of each MBI domain or MBI in NCI due to the small sample sizes and therefore were not able to replicate previous findings in the preclinical stages such as subjective cognitive decline.[9,13] Second, as it was suggested that age-related cognitive decline may span over decades,[37] we suspect that a longer follow-up duration may be required to capture the cognitive trajectory in milder stages. Third, as our cohort study commenced prior to the development of the MBI Checklist,[20] we operationalized 2 NPI assessments over 1 year for MBI diagnosis to match the criterion of persistent NPS. This approach may not have captured the breadth of MBI symptomatology described in the MBI Checklist, possibly resulting in a lower rate of MBI in our study. Lastly, our findings may not be generalizable to other Asian populations and would benefit from replications in other larger cohorts of Asian elderly from specialized clinics as well as the community.

To conclude, our study provides a holistic view of MBI by studying its clinical and cognitive profile and demonstrating its significance in longitudinal cognitive decline and disease progression in a Singaporean elderly cohort ranging from cognitively normal to moderately impaired. Our findings support the use of MBI evaluations complementary to neurocognitive assessments as a potential dementia preventive strategy.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.