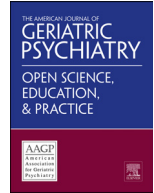


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Regular Research Article

Mild Behavioral Impairment is Associated With Incident Cognitive Decline Among Dementia-Free, Racially Diverse Older Adults: Data From the African Americans Fighting Alzheimer's in Midlife (AA-FAIM) Study

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ABSTRACT

Objectives: To determine whether MBI associates with worse cognitive performance over time and with incident cognitive decline in an older, racially/ethnically diverse cohort at early stages of cognitive change. **Design:** This observational cohort study followed participants from the Wisconsin Alzheimer's Disease Research Center Clinical Core (WADRC) for up to 13 visits. **Setting:** An urban university research center. **Participants:** Participants from the WADRC Clinical Core were included in this convenience sample if they were without dementia, had undergone at least 1 cognitive assessment, and completed measures of cognitive, clinical and affective function. **Measurements:** MBI was assessed using the Neuropsychiatric Inventory.

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Mild Behavioral Impairment is Associated With Incident Cognitive Decline Among

mild behavioral impairment (MBI)
neuropsychiatric symptoms
older adults
racially diverse

*Linear mixed effects models (LME) were fit to cognitive outcomes Trailmaking Tests A and B (TMT-A, B) and Wechsler Logical Memory (LM). Cox proportional hazard models assessed whether MBI was related to risk for incident global Clinical Dementia Rating Scale (CDR >0). **Results:** N = 584 participants with mean age 64.6 years, range 46-92.6 years, 59.4% female and 17% African American. LME results indicated participants with MBI exhibited worse age-associated decline on TMT-B, compared to those without MBI (beta=0.008, p = 0.01, CI: 0.002, 0.01, t(337) = 2.4, p = 0.01). MBI at baseline was associated with a significant hazard ratio (HR) indicating an increased risk of decline on the CDR (HR: 2.84; HR 95% CI: 1.68 — 4.81; p = 0.0001). **Conclusions:** MBI associated with worse cognitive performance and incident cognitive decline in a racially diverse, older adult sample at early stages of cognitive change. Increased awareness of the late life emergence of neuropsychiatric symptoms is warranted to assist in identification and improve prognostication and treatment of neurodegenerative disease. (The American Journal of Geriatric Psychiatry: Open Science, Education, and Practice 2025; 8:43–53)*

Highlights

- **What is the primary question addressed by this study?**

To determine whether Mild Behavioral Impairment (MBI) associates with worse cognitive performance and incident cognitive decline in a racially diverse older adult cohort in early stages of cognitive decline.

- **What is the main finding of this study?**

MBI is associated with worsening executive function even at earliest stages of cognitive decline. Among individuals without prior history of cognitive deficits, MBI associates with incident cognitive decline.

- **What is the meaning of the finding?**

Emergence of emotional or psychiatric symptoms in racially diverse older adults is associated with an adverse cognitive trajectory even at early stages of cognitive decline and implicates these symptoms as potential targets of intervention.

OBJECTIVE

Mild behavioral impairment (MBI), a syndrome describing persistent neuropsychiatric symptoms (NPS) acquired in late life¹ and associated with all-cause dementia^{2–5} is increasingly recognized as a frequent concomitant to accelerated cognitive decline.¹ Individuals with Mild Cognitive Impairment (MCI) who also present with MBI are more likely to progress to dementia and less likely to revert to normal than those without MBI.⁴ MBI comprises 5 behavioral categories: reduced motivation, affective dysregulation, impulse dyscontrol, social inappropriateness/rigidity, and abnormal perception or thought content.⁶ Symptoms in any category establish criteria for the disorder.

MBI is distinguishable from other mood/cognitive or neuropsychiatric disorders by the emergence of NPS (e.g. anxiety, depression, agitation, reduced tact, etc.) after the age of 50, persistence for at least 6 months and absence of dementia.¹

Symptoms of MBI appear to be common across the spectrum of cognitive decline, including earlier stages of disease. For example, among 1,377 nondemented individuals with cognition ranging from normal to MCI, 34.1% met criteria for MBI.⁷ Similarly, among 124 nondemented older adults in India, over half exhibited neuropsychiatric symptoms, and of these, almost 3-quarters met criteria for MBI. Prevalence of MBI was substantially higher in patients with MCI (48.9%) relative to those with subjective cognitive decline (SCD) (28.2%).⁸ Similarly, among cognitively normal participants included in the National

Alzheimer's Coordinating Center (NACC) dataset, the combined presence of MBI and subjective cognitive decline was associated with the highest risk of incident cognitive decline and progression to dementia relative to those without MBI.⁹ Indeed, individuals with MBI have been shown to perform more poorly on cognitive tasks regardless of their cognitive status.¹⁰ As a recently established syndrome, however, gaps are evident in our understanding of MBI.

First, compared to those diagnosed with MCI, less is known about MBI's association with cognitive function among individuals in the preclinical stages of neurodegenerative disease. Improving our knowledge in this domain is critical as it may portend clinically significant events and could enhance the identification and treatment of disease. One of the few studies that examined this relationship found that among cognitively normal participants, MBI was associated with progression to a clinical diagnosis of Alzheimer's dementia that was subsequently confirmed following postmortem exam as representing intermediate or high AD neuropathologic change according to the ABC criteria (ABC: amyloid plaque [A], neurofibrillary tangle stage [B] and neuritic plaque [C] score).¹¹ Additional studies that examine the association of MBI with cognitive decline and incident mild cognitive impairment would build upon this finding and provide additional insight on the clinical relevance of MBI.

Similarly, we must enhance our understanding of how MBI is expressed across ethnoracialized groups and not assume that it presents uniformly. For example, discrepancies have been described in how racialized groups express NPS. Specifically, subtle differences were noted in American Indian and African American participants' endorsement of depressive symptoms depending on the measure utilized.¹² This would suggest that there may be measurement differences in capturing NPS. It is also possible that the relationship between NPS symptoms and progression may be influenced by the cultural interpretations of these symptoms. These factors together may affect how NPS associate with disease progression.

For example, Black individuals with MBI-associated affective dysregulation were found to be significantly more likely to progress to dementia than non-Hispanic white participants with affective dysregulation.¹³ Similarly, Black participants with dementia are

more likely to exhibit NPS than non-Hispanic white participants with dementia.¹⁴ Taken together, additional studies are needed to characterize this syndrome in culturally and ethnoracially diverse samples.

With the goal of supporting early identification and treatment of ADRD across racialized groups, we attempted to help address these gaps. In a richly characterized sample comprised of older-middle aged non-Hispanic white, multiracial and Black/African American (AA) adults who were without dementia, we examined relationships between MBI and cognitive decline. We hypothesized that the presence of MBI would worsen cognitive performance over time and associate with incident cognitive and functional decline even at early stages of cognitive change.

METHODS

Participants

The analytic sample included older middle aged non-Hispanic white, multiracial, and Black/African American (AA) participants from the Wisconsin Alzheimer's Disease Research Center's (WADRC) Clinical Core. AA participants were additionally enrolled in African Americans Fighting Alzheimer's in Midlife (AA-FAIM), of the Wisconsin ADRC Clinical Core. AA-FAIM invests in community-engaged, programmatic recruitment and retention efforts¹⁵ while leveraging infrastructure from 2 ongoing longitudinal aging studies, the Wisconsin Registry for Alzheimer's Prevention (WRAP) and the Wisconsin ADRC. AA-FAIM pools harmonized data from participants self-identifying as Black to examine factors relevant to this population. Because measures of neuropsychiatric symptoms were not administered in both studies, only data from the Wisconsin ADRC were included in these analyses.

The ADRC Clinical Core enrolls adults aged 45-90 years spanning the AD continuum, with or without a family history of AD, and conducts annual study visits for cognitively normal older adults (>65 years) and MCI participants (≥ 45 years); biennial visits are conducted for cognitively normal participants aged 45-65. Participants with dementia (≥ 45 years) are studied annually if they agree to visits beyond the initial study visit. Regardless of cognitive status, individuals

must have a study partner to be enrolled in the study. Clinical status (cognitively normal/unimpaired, impaired-other, mild cognitive impairment [MCI] or dementia) is adjudicated during consensus conference for each subject at each visit. Diagnoses of MCI or dementia due to suspected AD or another cause are assigned based on NIA-AA criteria^{16, 17} without reference to biomarkers. For these analyses, only participants without diagnoses of dementia were included. All participants had at least 1 qualifying cognitive assessment and completed measures of cognitive, clinical and affective function. Participants were followed between 1 and 13 visits; mean number of visits was 5, with a mean of 1.5 years between visits.

MBI Derivation

The Neuropsychiatric Inventory Questionnaire (NPI-Q)¹⁸ was administered to the participant's study partner at each Wisconsin ADRC Clinical Core visit. Persistent MBI was derived from the NPI-Q following Ismail et al.¹ and coded as present or absent. Study partners completed the NPI-Q by rating neuropsychiatric symptoms as present or absent and indicating symptom severity. A baseline MBI rating (present/absent) was derived using study partners' report of neuropsychiatric symptoms at 2 consecutive visits, (i.e., 2 consecutive MBI scores >0 = MBI present). Baseline visit was defined as the visit at which persistent MBI was first detected (i.e. the visit at which the participant had a consecutive positive MBI score). For participants without persistent MBI, baseline was defined as their second visit.

Cognitive Measures

Cognitive tasks were administered to the participant at each Wisconsin ADRC Clinical Core visit. The executive functions, processing speed and mental flexibility were assessed with the Trailmaking Tests A and B (TMT-A, TMT-B).¹⁹ Score is measured by completion time; thus, a lower score indicates (faster) better performance. Verbal learning and recall were measured using Wechsler Memory Scale Logical Memory Test,²⁰ Immediate and Delayed Recall scores. The task involves oral presentation of a brief story, which participants repeat immediately and again after a 20-30 minute delay.

Clinical Dementia Rating Scale:²¹

The Clinical Dementia Rating Scale (CDR) is a semi-structured, clinical interview-based diagnostic tool conducted with an informant who knows the participant well. It assesses cognitive and functional abilities in 6 different domains, including memory, judgement and problem solving, orientation, home and hobbies, community affairs, and personal care. An indication of cognitive or functional decline in any domain results in a global score of >0.

Analyses

We used independent sample t-tests or chi-square tests as appropriate to compare demographic characteristics across MBI groups. Separate linear mixed effects models with random intercepts and slopes were fit to 4 cognitive outcomes: TMT-A and TMT-B (log transformed), and Wechsler Memory Test-Logical Memory Immediate and Delayed Recall. Each model included persistent MBI, time and the interaction between persistent MBI and time as the predictors of interest. Time was measured using participant age centered around mean baseline age. Covariates included participant sex, education level (high school or less vs more than high school), racialized group (3-level categorical variable: non-Hispanic White, Black or African American, and a multiracial category comprised of individuals identifying as American Indian/AK Native, Asian, or racial group unknown), total visits to account for practice effects, and baseline clinical diagnosis (MCI, impaired not MCI, or unimpaired). The statistical significance of model terms was calculated using Satterthwaite's t-test. To address potential confounds of associations between cognitive impairment and MBI, an additional sensitivity analysis was conducted removing baseline MCI participants. LME models were fit using the package lme4²² in R.²³

Cox proportional hazard models were used to assess the association between baseline MBI and age to first global CDR >0 occurrence, while controlling for common covariates (baseline diagnosis, baseline education category, and self-identified sex and race). Inference on regression coefficients was conducted using the Wald test. A hazard ratio (HR) significantly greater than 1.0 would suggest that MBI increases the risk for progression to cognitive impairment. All covariates were included as nonstratified

independent variables, except education category (\leq HS vs. $>$ HS), which was used as strata for the baseline hazard function to address issues of nonproportionality in education (other covariates had no major concerns for proportionality assumption). Ideally, we would examine racialized groups independently; however, using separate categories for minoritized groups as defined above resulted in small sample sizes and proportionality issues. For this reason alone, hazard models compared risk for non-Hispanic white participants to risk for all other self-reported racialized categories combined. This is in no way meant to imply that any racialized group represents a gold standard.

Models used a variable entry setup in which participants entered the risk pool at their baseline age and exited the risk pool at their age at last visit if no event occurred (censored), or at their age at first event (i.e., global CDR $>$ 0) occurring after baseline. Baseline for these models was defined as the first visit at which persistent MBI could be determined (i.e., after at least 2 visits), or at the second visit for participants without MBI. Participants were included if their CDR=0 at baseline and they had at least 1 follow-up visit. Note that it is possible for participants to receive a consensus conference diagnosis of MCI but have a CDR=0. Graphical examination of the Cox-Snell residuals vs the Nelson-Aalen cumulative hazard estimate indicated the models reasonably fit the data. Due to the relatively small risk pool at ages $<$ 60 years, the few number of events in the MBI positive subgroup at the younger ages represented a relatively large proportion of that participant pool. For this reason, a sensitivity analysis was conducted with the additional requirement that baseline/study entry be \geq 60 years. Cox regression models were fit in R using the *survival*²⁴ and *coxph* packages.²⁵

In a subset analysis, we assessed the impact of MBI in CDR progression among Black/ African American participants. Given the small number of events in this subgroup, a Cox proportional hazard model was fitted with inclusion of MBI as the sole covariate.

RESULTS

Baseline participant ($N = 584$) characteristics by MBI status are shown in Table 1. Participants were relatively young (mean age = 64.6, SD = 9.4), female

(59.4%) and well educated (86.5% had at least some college education). Approximately 17% of the sample was Black/African American. Additionally, 41.8% of participants carried at least 1 APOE ϵ 4 allele, signifying a greater risk of developing Alzheimer's disease. Approximately 15% of participants were diagnosed with MCI, while 4% exhibited some cognitive impairment but did not meet criteria for MCI. The large majority of participants (81.3%) were cognitively normal at baseline.

Thirty-three percent of the participants met the criteria for persistent MBI ($n = 194$). Participants with persistent MBI were significantly older (mean = 68.5 years, range = 9.1 years) than those without MBI (mean 62.7 = years, range = 8.9 years). Notably, individuals without any evidence of persistent MBI were significantly more likely to be cognitively normal (90.5%) than those with persistent MBI (62.9%).

Regression coefficients (Est), 95%CI, t (df) and p -values for predictors of interest are shown in Table 2. Linear mixed effects analyses revealed that the presence of MBI was significantly associated with a declining cognitive trajectory over time on a measure of executive function. Specifically, participants who demonstrated persistent MBI exhibited worse age-associated decline in TMT-B (log-transformed) compared to those without MBI ($Est = 0.008$, $t(337) = 2.4$, $p = 0.01$, see Fig. 1). Based on simple slopes calculation, the age related decline in performance in TMT-B performance was slightly more pronounced in those with MBI ($b = 0.028$, $t(96)=9.1$, $p < 0.001$) compared to those without ($b = 0.019$, $t(273)=10.7$, $p < 0.001$). The MBI X Time interaction remained significant ($Est= 0.008$, $t(285)=2.0$, $p = 0.03$) after excluding cognitively impaired participants. By contrast, the presence of persistent MBI did not significantly moderate age-related cognitive change on measures of simple processing speed (TMT- A, $Est= 0.01$, $t(337)=2.4$, $p = 0.11$) or memory (Logical Memory Immediate, $Est= -0.04$, $t(345)=1.45$, $p = 0.19$ or Delayed recall, $Est= -0.03$, $t(339)=0.84$, $p = 0.37$).

Persistent MBI at baseline was also associated with an increased hazard ratio of cognitive/functional decline as measured by incident CDR $>$ 0 (HR: 2.84; HR 95% CI: 1.68 — 4.81; $p = 0.0001$) in the first model with all subjects (see Fig. 2). Individuals with MBI were 3 times more likely to progress to a CDR $>$ 0 and exhibited a steeper rate of cognitive decline than those

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TABLE 1. Participant Characteristics by Persistent MBI Status

MBI Total Sample	Absent (N = 390)	Present (N = 194)	Total (N = 584)	χ^2 (df), p Value
Baseline diagnosis				65.9 (2), < 0.001
Impaired, not MCI	10 (2.6%)	14 (7.2%)	24 (4.1%)	
MCI	27 (6.9%)	58 (29.9%)	85 (14.6%)	
Normal	353 (90.5%)	122 (62.9%)	475 (81.3%)	
Sex				1.69(1), 0.193
Female	239 (61.3%)	108 (55.7%)	347 (59.4%)	
Male	151 (38.7%)	86 (44.3%)	237 (40.6%)	
Racialized category				4.23(2), 0.121
Black/AA	61 (15.6%)	39 (20.1%)	100 (17.1%)	
Multiracial URG	19 (4.9%)	15 (7.7%)	34 (5.8%)	
White	310 (79.5%)	140 (72.2%)	450 (77.1%)	
Hispanic ethnicity				0.29(2), 0.862
No	382 (97.9%)	189 (97.4%)	571 (97.8%)	
Yes	4 (1.0%)	2 (1.0%)	6 (1.0%)	
Unknown	4 (1.0%)	3 (1.5%)	7 (1.2%)	
Education				6.28(1), 0.012
HS or less	43 (11.0%)	36 (18.6%)	79 (13.5%)	
Some college or more	347 (89.0%)	158 (81.4%)	505 (86.5%)	
APOE				3.53(1), 0.067
0 risk alleles	229 (60.9%)	101 (52.9%)	330 (58.2%)	
1 or more risk alleles	147 (39.1%)	90 (47.1%)	237 (41.8%)	
Baseline age				5.2(161) ^a < 0.001
Mean (SD)	62.7 (8.9)	67.7 (9.1)	63.6 (9.4)	
Range	46.04 - 92.6	46.7 - 89.0	46.0 - 92.6	
Informant				5.33, 0.070
Spouse/Partner	259 (66.4%)	129 (66.5%)	388 (66.4%)	
Offspring	35 (9.0%)	28 (14.4%)	63 (10.8%)	
Other	96 (24.6%)	37 (19.1%)	133 (22.8%)	

Notes. Baseline MBI defined as present when study partner reports on a standardized questionnaire indicated the presence of elevated behavioral and psychiatric symptoms at 2 consecutive study visits. The instrument, the Neuropsychiatric Inventory Questionnaire (NPI-Q) asks study partners to rate a symptom as present or absent and to indicate severity. A score of >0 at 2 consecutive study visits was used to designate baseline MBI present. Group differences were tested using Pearson’s Chi-squared test for categorical variables.

^aGroup differences in mean age at baseline were tested using Welch’s independent samples t-test. Abbreviations: MBI: mild behavioral impairment, MCI: mild cognitive impairment, AA: African American, URG: under-represented group (American Indian, Alaskan Native, Asian), HS: high school, APOE: apolipoprotein E ϵ 4 allele.

without MBI. A similar model including only Black/AA participants did not demonstrate significance, but this may have been due in part to the much smaller sample ($n = 100$, 39 with persistent MBI). Although

not statistically significant, the estimated effect of MBI was similar in this model compared to the all-participants model (HR: 2.72; HR 95% CI: 0.72–10.34; $p = 0.14$).

TABLE 2. Results From Linear Mixed Effects Models

	(log) Trails B			(log) Trails A			Logical Memory Immediate Recall			Logical Memory Delayed Recall		
	Est	95% CI	t(df), p	Est	95% CI	t(df), p	Est	95% CI	t(df), p	Est	95% CI	t(df), p
MBI	0.07	0.004, 0.13	2.2(536), 0.03	0.07	0.02, 0.12	2.5(519), 0.01	-0.28	-0.87, 0.28	0.96(555), 0.34	-0.63	-1.3, 0.01	1.8(537), 0.06
Age	0.02	0.01, 0.02	10.7(365), < 0.001	0.01	0.01, 0.02	8.9(354), < 0.001	-0.001	-0.04, 0.03	0.5(365), 0.96	0.02	-0.02, 0.06	0.99(357), 0.39
MBIxAge	0.008	0.002, 0.01	2.4(337), 0.01	0.005	-0.001, 0.01	1.7(329), 0.11	-0.04	-0.10, 0.02	1.44(345), 0.19	-0.03	-0.10, 0.04	.844(339), 0.37

Covariates included sex, education level (<12 years or ≥ 12 years), self-reported racial category, baseline diagnosis, and total visits (i.e. practice effects). Age centered on baseline age is the measure of time. MBI is a categorical indicator (ref: Absent). Models were fit to $N = 1,960$ observations from 572 unique participants. Significance for fixed effects was calculated using Satterthwaite’s t-test.

FIGURE 1. Performance on (log) trails B across time by persistent MBI status. Note: Slopes were calculated for a cognitively unimpaired non-Hispanic, White female participant with ≥ 12 years education and an average number of study visits. After stratifying by MBI, the simple age slope for participants with and without MBI = 0.028 and 0.019 respectively. Shading around each regression line represents the 95% CI.

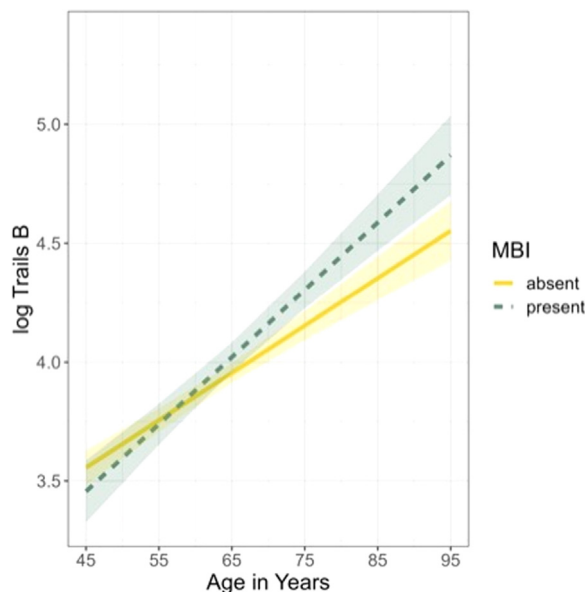
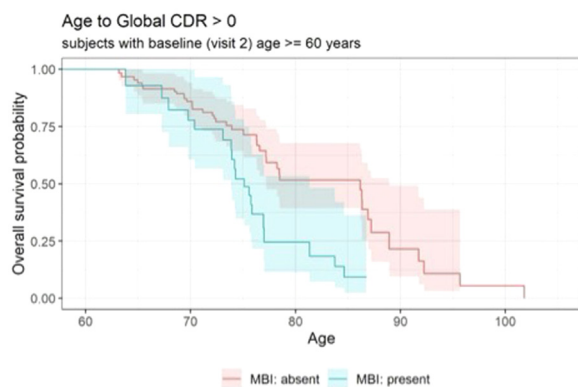


FIGURE 2. Kaplan Meier survival curve of age to incident cognitive decline on the Clinical Dementia Rating Scale stratified by MBI category. Note: Shading around each HR line represents the 95% CI.



In Cox model sensitivity analyses, MBI results were stable and consistent. Removing participants with baseline ages < 60 years resulted in 207 fewer participants (13 of whom had progressed to $CDR > 0$), and the presence of MBI remained positively associated with risk of progression to $CDR > 0$ (HR: 2.27; HR 95% CI: 1.26–4.18; $p = 0.0067$). Similarly, when we excluded participants with an MCI diagnosis and $CDR = 0$ at baseline, ($n = 4$, 3 of whom progressed to $CDR > 0$), presence of MBI remained associated with risk of progression to $CDR > 0$ (HR: 2.95; HR 95% CI: 1.73–5.04; $p = 0.0001$).

CONCLUSIONS

In a relatively young, nondemented sample comprised of individuals identifying as non-Hispanic white, Black/African American and multiracial, the presence of MBI was associated with modest but statistically significantly worse age-associated decline in executive function. More importantly, the rate of progression to $CDR > 0$ was 3 times higher in participants with MBI at baseline than participants with no MBI, a finding of meaningful clinical significance. These results reflect the close interconnection between cognitive performance and affective/behavioral function and may have important implications for timely identification and treatment of neurodegenerative disease.

Our findings represent some of the first to examine MBI in a well characterized sample including a sizable group of Black/AA participants, and they demonstrate the relatively high prevalence of the MBI syndrome among both non-Hispanic white and Black/AA participants. Performance on TMT-B, an executive function measure of complex processing speed and mental set shifting, declined faster over time for participants exhibiting persistent MBI compared to those without MBI. Based on our results, a person with MBI would be expected to take approximately 1sec/yr longer to complete TMT B than a person without MBI, a difference of only modest clinical significance. Considerably more concerning from a clinical standpoint is the increased hazard of incident cognitive decline associated with MBI, as individuals with MBI exhibited a 3 times higher rate of progression to cognitive impairment on the CDR relative to those without MBI. Moreover, those with MBI displayed a steeper rate of cognitive decline than those

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with no MBI. Our findings suggest that MBI may represent an important risk factor for cognitive decline even at the earliest stages of disease. If replicated, our results suggest that assessment of MBI could serve as a powerful tool for the timely detection of subtle cognitive decline in diverse groups. The addition of a measure of MBI to a simple task of executive function is noninvasive and cost-effective and could facilitate identification of those individuals at greater risk for progression to cognitive impairments. These results contribute to the much-needed exploration of MBI among participants whose backgrounds reflect diverse social determinants of health, such as different ethnoracialized identity, socio-economic status, neighborhood disadvantage, etc. Strengths of our study included our enrollment of an ethnoracially diverse and well-characterized cohort, and longitudinal analyses supported by robust follow-up of up to 13 visits per participant.

Still, questions remain regarding the relationship between cognitive decline and late life neuropsychiatric symptoms. For example, the causal direction of the link between the phenomena remains unclear. It is possible that the presence of MBI leads to executive dysfunction or cognitive impairment more generally; other studies have found associations between MBI and processing speed, executive function and memory.^{10,26,27} MBI comprises 5 subcomponents of affective function: decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness/rigidity, and abnormal perception or thought content.²⁸ Each of these subdomains may play a role in optimal cognitive function, and weaknesses in any of these areas could contribute to diminished cognitive performance. With specific regard to TMT-B, performance on this complex task depends on highly efficient visual and psychomotor processing speed and mental flexibility, requiring individuals to inhibit rehearsed patterns and switch back and forth between 2 sequences;²⁹ each may be impacted by affective dysfunction. Specifically, reduced motivation or apathy could result in poor effort and lower score.³⁰ Symptoms of anxiety or depression could lead to discouragement and inefficient or poorer performance,^{31,32} impulse dyscontrol could be associated with failure to maintain task set; excessive rigidity could reduce ability to easily shift sets; and abnormal perception could lead to internal distraction and inability to maintain the task.³³

Alternatively, the development of cognitive decline may engender affective dysregulation or affective and cognitive performances may demonstrate bi-directional or reciprocal associations. The novel experience of emerging deficits in previously strong cognitive skills could elicit feelings of anxiety, apathy, depression, agitation, fear of failing,³⁴ etc. Older adults have been found to endorse worry about developing psychiatric symptoms within the context of cognitive decline.³⁵

Additionally, it is possible that common underlying disease pathologies associated with MCI and dementia are driving both affective and cognitive effects simultaneously, such that MBI may represent a prodromal stage of Alzheimer's disease or similar neurodegenerative syndromes.³⁶ This notion is supported by the fact that our participants with persistent MBI were significantly older than those without symptoms. Age is associated with higher levels of neuropathologies including amyloid and tau proteinopathies,³⁷ although associations with neuropathology biomarkers were not assessed in the current analyses. Both beta amyloid³⁸ and tau³⁹ levels have been found to be associated with MBI. Moreover, a recent review of relevant neuroimaging findings reveal that MBI is associated with atrophy in the medial and lateral temporal and frontal lobes, as well as with white matter hyperintensities, and default mode and salience mode networks.⁴⁰ Future studies of MBI should incorporate biomarkers such as beta amyloid, tau, alpha synuclein, vascular disease, neuroinflammation, neuroimaging, and others to clarify causal and directional relationships between physiological and cognitive/behavioral markers of disease.

In our models, we did not find significant associations between MBI and performance on TMT-A or memory tasks. Previous studies have shown mixed results with regard to relationships between MBI, processing speed and memory performance, with some studies finding MBI predicted declines in processing speed, executive function and memory,²⁷ while others found no associations between MBI and episodic memory.³⁹ It may be that underlying neuropathology plays a role in mediating the effect of MBI and cognitive function and that our relatively young and largely healthy participants show only subtle changes. Further investigations are needed to better understand the relationship between MBI and different domains of cognitive function. Such knowledge

could inform future symptom management, for example in informing the selection of antidepressant versus antiamyloid therapy. Because cognition and affective function are so closely linked, future studies should investigate whether providing social and emotional support to individuals with MBI results in improved cognitive performance. Alternatively, facilitating optimal cognitive performance may be associated with stronger affective regulation.

With a relatively ethnoracially diverse sample, we are much more confident that our findings are reliable and meaningful to the population at large. It is imperative that research groups recruit participants from diverse backgrounds, including ethnoracialized identities in order to support the broad dissemination of findings. Given that Black/African Americans currently comprise 14.4% of the United States population⁴¹ and that the world population is less than half non-Hispanic white, we can no longer default to completely non-Hispanic white samples.

There are still limitations with our analyses. Since we had limited information on participants' psychiatric health which did not include age of onset, we chose to not to attempt to control for possible confounding depression. However, the definition of MBI specifies onset in older adulthood and the NPI-Q instructions ask informants to report on new behaviors (since experiencing memory problems) observed in the last month.

Our cohort was ethnoracially representative for the number of individuals identifying as Black/African American but it was not representative in other ways. Individuals opting into research- convenience samples- are not typical of the general population and these results may not generalize to individuals from more disadvantaged backgrounds.⁴² We also note that racial and ethnic disparities in the diagnosis of cognitive and neuropsychiatric disorders may contribute to skewed results. By over diagnosing behavioral symptoms in under-represented groups, participants may be under-included in studies of MBI, in which neuropsychiatric symptoms can be diagnosed only in late life. Racial disparities have been documented in the diagnosis and treatment of depression,⁴³ and other mental illnesses. Blacks are also more likely than whites to be diagnosed with schizophrenia-spectrum disorders, in part secondary to racial bias among clinicians.⁴⁴⁻⁴⁶ Indeed, the

American Psychiatric Association recently issued a formal apology for its contribution to systemic racism⁴⁷ by its pathologizing of individuals identifying as a member of a racialized group. For future studies to be fully inclusive, ongoing attention is needed to account for potential misdiagnosis of neuropsychiatric symptoms in ethnically and racially minoritized groups.

To conclude, we found that MBI was associated with both worsening cognitive performance over time and incident cognitive decline in a relatively young, largely non-Hispanic white and Black/AA, non-demented sample. The emergence of late life neuropsychiatric symptoms merits increased consideration to facilitate understanding of disease course and to guide treatment. As clinicians, researchers and caregivers, it is critical that we attend to the broad array of factors that influence function in both cognitive and behavioral domains to fully support our patients.

CONSENT STATEMENT

Study participants provided consent prior to all study visits. Study procedures were approved by the University of Wisconsin-Madison Institutional Review Board.

DISCLOSURES

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Diane Gooding serves as deputy editor for Psychiatry Research. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This work is supported by the National Institutes on Aging: NIA AA-FAIM NIA grant to Dr. Carey Gleason for African Americans Fighting Alzheimer's in Midlife (AA-FAIM): 1R01AG054059-01, NIA-ICARE: R01 AG062307, NIA AMICA R01 AG074231, and Wisconsin Alzheimer's Disease Research Center grant P30 AG062715, NIA RFAG027161. The NIH had no role in study design, data collection analysis, interpretation, writing, or decision to submit for publication. Dr. Gleason is currently receiving grants AG054059, AG062307, AG074231 from the National Institute of Health. Dr. Ennis is current receiving funding from the

AUTHORS CONTRIBUTION STATEMENT

Barbara L. Fischer: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. Carol A. Van Hulle: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. Derek L. Norton: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. Mary F. Wyman: Writing – review & editing. Gilda Ennis: Writing – review & editing. Nickolas H. Lambrou: Writing – review & editing. Shenikqua Bouges: Writing – review & editing. Diane C. Gooding: Writing – review & editing. Carey E. Gleason: Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

DATA SHARING

This data is available upon request. No use of AI was included in the writing of this manuscript. These data were orally presented at the Alzheimer's Association International Conference (AAIC) on July 28, 2024.

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