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

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Abstract

Background: Mild behavioral impairment (MBI) and subjective cognitive decline (SCD) are dementia risk states, and potentially represent neurobehavioral and neurocognitive manifestations, respectively, of early stage neurodegeneration. Both MBI and SCD predict incident cognitive decline and dementia, are associated with known dementia biomarkers, and are both represented in the NIA-AA research framework for AD in Stage 2 (preclinical disease).

Objective: To assess the associations of MBI and SCD, alone and in combination, with incident cognitive and functional decline in a population of older adults. We tested the hypothesis that MBI and SCD confer additive risk for decline.

Methods: Cognitively normal participants were followed up annually at Alzheimer’s Disease Centers. Logistic regression assessed the relationship between baseline classification (MBI-SCD-, MBI-SCD+, MBI+SCD-, or MBI+SCD+) and 3-year outcome.

Results: Of 2,769 participants (mean age = 76), 1,536 were MBI-SCD-, 254 MBI-SCD+, 743 MBI+SCD-, and 236 MBI+SCD+. At 3 years, 349 (12.6%) declined to CDR > 0, including 23.1% of the MBI+ group, 23.5% of the SCD+ group, and 30.9% of the intersection group of both MBI+ and SCD+ participants. Compared to SCD-MBI-, we observed an ordinal progression in risk (ORs [95% CI]): 3.61 [2.42–5.38] for MBI-SCD+ (16.5% progression), 4.76 [3.57–6.34] for MBI+SCD- (20.7%), and 8.15 [5.71–11.64] for MBI+SCD+ (30.9%).

Conclusion: MBI and SCD together were associated with the greatest risk of decline. These complementary dementia risk syndromes can be used as simple and scalable methods to identify high-risk patients for workup or for clinical trial enrichment.

Keywords: Mild behavioral impairment, mild cognitive impairment, neuropsychiatric symptoms, preclinical Alzheimer’s disease, subjective cognitive decline

INTRODUCTION

Commonly cited reasons for high costs and poor outcomes in Alzheimer’s disease (AD) clinical trials are screen failures and poor recruitment of early...
phase illness [1, 2]. Identification of sensitive and specific premorbid indicators of emergent pathology is a priority [1]. A leading strategy to detect preclinical disease is to focus on subjective cognitive decline (SCD), a perceived decline in cognitive ability in the absence of objective findings [3, 4], which has been associated with amyloid burden [5] and incident cognitive decline and dementia in some [6].

An emerging strategy is to capture early behavioral manifestations of dementia [7] that occur in 30% of AD patients prior to cognitive manifestations [8]. Mild behavioral impairment (MBI) is a validated syndrome that serves as a sensitive transitional state marker for dementia syndromes. MBI is characterized by the emergence in later life of persistent neuropsychiatric symptoms (NPS), and may be an index manifestation of dementia, evident before cognitive symptoms [9]. MBI is associated with cognitive impairment and incident cognitive decline and dementia [10–17], as well as known dementia markers including amyloid-β [18], tau [19, 20], neurofilament light [21], temporal lobe atrophy [22, 23], frontal lobe atrophy [24], white matter atrophy [25], functional dysconnectivity [26, 27], and AD genetic loci [28, 29]. This body of evidence suggests that in some older adults, MBI may be a consequence of emerging dementia proteinopathies which manifest independently or in concert with cognitive symptoms. What remains unclear is whether these constitute independent or synergistic prodromal manifestations with clinical utility for early detection and intervention.

Reflecting early behavioral and cognitive signals for dementia, both MBI and SCD are included in the NIA-AA AD research framework in Stage 2 as potential preclinical manifestations of underlying neuropathology (Table 1, Fig. 1) [30]. To our knowledge, there have been no large prospective studies examining the prognostic utility of MBI and SCD in a sample of objectively normal individuals at higher risk for dementia. We hypothesized that cognitive and behavioral changes in late life may represent coherent or divergent manifestations of emerging pathology that can be leveraged to identify sensitive windows for intervention.

**MATERIALS AND METHODS**

**Source population: National Alzheimer’s Coordinating Center (NACC)**

Data used in this study were obtained from the NACC database (https://www.alz.washington.edu/). NACC was established by the National Institute on Aging (NIA) and consists of multiple NIA-funded...
Alzheimer’s Disease Research Centers (ADRCs) recruiting and collecting data on subjects with cognitive function ranging from normal to dementia. The NACC Uniform Data Set (UDS) is a large longitudinal dataset that includes demographic and standardized clinical data collected approximately annually. All test centers administered standardized forms and informed consent was collected from all subjects and their informants. Detailed information on the cohort and neuropsychological battery of tests included in UDS is described elsewhere [31–33]. NACC-UDS with a December 2018 data freeze date was used for this study.

**Patient groupings**

MBI status was derived from UDS using a published algorithm [34, 35] for transformation of the Neuropsychiatric Inventory Questionnaire (NPI-Q) [36] items to MBI domains. Specifically, ten NPS domains from the NPI-Q were used to populate the five MBI domains of decreased motivation (NPI-Q apathy/indifference); emotional/affective dysregulation (NPI-Q depression/dysphoria, anxiety, elation/euphoria); impulse dyscontrol (NPI-Q agitation/aggression, irritability/lability, aberrant motor behavior); social inappropriateness (NPI-Q disinhibition); and abnormal perception or through content (NPI-Q delusions, hallucinations). To obtain the MBI total score, these five transformed domain scores were added together. As the NPI-Q has a reference range of one month. Thus, to approximate MBI persistence of symptoms criteria, individuals with MBI total score >0 at two consecutive annual visits were classified as MBI positive (MBI+) and their MBI scores were calculated as the average over the interval. Those with no NPS were classified as MBI negative (MBI-) for comparison.

To determine subjective cognitive decline, the SCD-Initiative Workgroup criteria [3] were used as a framework and operationalized in NACC as follows: 1) endorsement by participant of a decline in memory on the UDS B9 form; and 2) normal cognition.

Figure 2 shows the step-by-step process for participant inclusion/exclusion. All NACC participants from 2005–2018 were initially considered for inclusion. The initial step was to classify based on MBI status (MBI+/−) and those with transient NPS not meeting MBI duration criteria were excluded. Study endpoint was chosen a priori to be 3 years to reflect clinical practice and design of observational cohort studies. This approach provided a concrete time frame to assess change, in order to balance the need to wait long enough to see change, but to also minimize attrition that would accrue due to age-related mortality and other diseases that confound cognitive assessments. We included participants with a follow-up visit ~3 years after the baseline visit to evaluate the change in Clinical Dementia Rating Scale (CDR® Dementia Staging Instrument) [37] score over time and participants were excluded if they were missing the 3-year study visit. SCD status was then determined and participants with a baseline CDR > 0 were excluded. Finally, those with a baseline diagnosis of a psychiatric illness were excluded.

**Study variables**

Baseline variables included age, sex, education, and MBI/SCD category. Our primary outcome measure, the CDR, consists of six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, assessed by objective testing and informant report [37]. In our study, we used the global standard CDR score, which assesses the level of impairment, and ranges in severity from no impairment (CDR 0), questionable impairment (CDR 0.5 —corresponding roughly to MCI), mild impairment (CDR 1 — corresponding to mild dementia), to moderate to severe impairment (CDR 2-3). All participants had a baseline CDR score of 0, and we measured a change in cognition and function to a CDR > 0 at 3 years.

**Standard protocols, registrations, and patient consent**

The NACC database itself is exempt from IRB review and approval because it does not involve human subjects, as defined by federal and state regulations. However, all contributing ADRCs obtained informed consent from their participants and maintained their own separate IRB review and approval from their institution prior to submitting data to NACC.

**Data availability statement**

Data is available upon request from the corresponding author (ZI).

**Statistical analysis**

Categorical variables were analyzed with $\chi^2$ test, and the continuous variables were analyzed using one-way ANOVA. We defined patient groups ordinally
Fig. 2. Flowchart of participants from NACC included for analysis.
according to the absence or presence of SCD, MBI, or both at baseline. Cognitive and functional decline was defined as progression to CDR > 0 after 3 years. We tested the ordinal association of patient groups and cognitive and functional decline using linear by linear association and Somers’ D [38]. Ordinal approaches permit explicit testing of an ordinal association in the probability distribution for progression to dementia across groups. As our theoretical model posits SCD and MBI as independent axes of dementia risk, the ordinal rank of SCD + MBI- and SCD-MBI + is arbitrary between SCD-MBI- and SCD + MBI+, and therefore both permutations were tested. It is similarly worth noting that the hypotenuse in SCD*MBI space, or dementia risk space, is not expected to be additive according to our theoretical model.

We also computed odds ratios (OR) for cognitive and functional decline using logistic regression with the patient group having neither SCD nor MBI (SCD-MBI-) at baseline serving as the reference group. In this model, we included terms for all variables reaching statistical significance ($p < 0.05$) in the univariate analyses to calculate Adjusted Odds Ratios (AOR). All analyses were conducted in SPSS v24 (IBM Corporation) with $\alpha$ set at 0.05.

**RESULTS**

The final sample consisted of 2769 participants with CDR 0 at baseline. Participants had neither MBI nor SCD (MBI-SCD-; $n = 1536$); SCD but no MBI (MBI-SCD+; $n = 254$); MBI but no SCD (MBI+SCD-; $n = 743$); and both MBI and SCD (MBI + SCD+; $n = 236$). There were significant differences in sex, age, ethnicity, and a history of hypertension but no significant differences regarding any other clinical and demographic characteristic investigated (Table 2).

Over the 3 years of follow-up, 349/2769 (12.6%) individuals had evidence of cognitive and functional decline. In Fig. 3, we present the incidence of decline according to the baseline presence of MBI, SCD, or their combination. Of the 1536 MBI-SCD- participants, 80 (5.21%) progressed to CDR > 0 at 3 years, while progression for MBI-SCD+ was 42/254 (16.54%), MBI + SCD- was 154/743 (20.73%), and MBI + SCD+ was 73/236 (30.93%). This highly significant difference (linear-by-linear $\chi^2 = 193.24$, df = 1, $p < 0.001$) also revealed a strong ordinal by ordinal symmetry (Somers’ $D = 0.22$, SE = 0.015, Approximate $T = 12.62$, $p < 0.001$), which held whether...
the order of SCD + MBI- or SCD-MBI + was reversed (linear-by-linear $\chi^2 = 160.41$, df = 1, $p < 0.001$; Somers’ $D = 0.21$, SE = 0.015, Approximate $T = 12.25$, $p < 0.001$).

To quantify the increased risk of incident cognitive and functional decline according to these baseline risk definitions, we used logistic regression to generate adjusted odds ratios (AOR) and 95% confidence intervals (CI). The odds of change to CDR $> 0$ was 8.15 times higher for MBI + SCD + than MBI-SCD- (95%CI 5.71–11.64, $p < 0.001$; AOR = 7.87, 95%CI: 5.46–11.35, $p < 0.001$). Those with MBI + SCD- had 4.76 times the odds of increased CDR than MBI-SCD- individuals (95%CI 3.57–6.34, $p < 0.001$; AOR = 4.26, 95%CI: 3.17–5.73, $p < 0.001$). Those with MBI-SCD + had 3.61 times the odds of increased CDR than MBI-SCD- individuals (95%CI 2.42–5.38, $p < 0.001$; AOR = 3.30, 95%CI: 2.20–4.96, $p < 0.001$). Covariates for all models were age, sex, race, and history of hypertension.

We then examined the distribution of CDR scores at follow-up according to the presence of SCD, MBI, or both at baseline (Fig. 4), which revealed that the magnitude of progression from CDR 0 increased incrementally according to baseline characteristics. This distribution in CDR scores was significantly different across groups (linear-by-linear $\chi^2 = 165.96$, df = 1, $p < 0.001$), with strong ordinal by ordinal symmetry (Somers’ $D = 0.22$, Approximate $T = 12.69$, $p < 0.001$). This also held when the order of SCD + MBI- and SCD-MBI + was reversed (linear-by-linear $\chi^2 = 116.32$, df = 1, $p < 0.001$; Somers’ $D = 0.21$, Approximate $T = 12.32$, $p < 0.001$).

Over the 3 years of follow-up, 2/1536 of the MBI-SCD- participants (0.1%) progressed to CDR $\geq 1$ (dementia), compared to 1/254 of the MBI-SCD + participants (0.4%), 20/743 of the MBI + SCD- participants (2.7%), and 3/236 of the MBI + SCD + participants (1.3%) (Fig. 5). To quantify this increased risk of incident dementia over the follow-up period, we used logistic regression. Compared to MBI-SCD-, the odds of progressing to dementia over the follow-up period were 21.21 (95%CI: 4.94–91.01, $p < 0.001$; AOR = 19.23, 95%CI: 4.40–84.03, $p < 0.001$) for MBI + SCD- and 9.87 (95%CI: 1.64–59.41, $p < 0.05$; AOR = 9.33, 95%CI: 1.53–56.78, $p < 0.05$) for MBI+SCD+individuals. Covariates for all models were age, sex, ethnicity, and history of hypertension.

**DISCUSSION**

In an analysis of a longitudinal cohort of 2,769 participants, we demonstrated that those who are cognitively unimpaired, have MBI, SCD, or both MBI and SCD lie on a continuum of risk for incident cognitive decline and dementia. Importantly, MBI was associated with progression to CDR $> 0$ at the three year visit even when cognitive symptoms were absent (i.e., in the absence of SCD). The OR for progression to CDR $> 0$ was numerically higher in persons with MBI alone (20.7% progression rate; OR 4.76) compared with SCD alone (16.5% progression rate; OR 3.76) but this difference was not statistically significant. Of all the MBI + participants, 23.19% progressed from CDR 0 to CDR $> 0$ at 3 years, compared to 23.5% of the total SCD + group, and 30.9% of the intersection group of both MBI + and SCD + . MBI was also associated with progression from normal cognition to dementia (CDR $\geq 1$), with very high ORs (OR of 19.23 for MBI alone and 9.87 for MBI + SCD + ) but these analyses were based on
only a handful of events and consequently specific estimates are likely unstable.

**Nosology of psychiatric symptoms**

Chronic and recurrent psychiatric syndromes are associated with an increased risk of dementia [39, 40]; however, *de novo* persistent psychiatric symptoms in older age constitute a unique risk marker. In order to restrict our approach to this population, we excluded participants with a psychiatric diagnosis at baseline as MBI diagnosis is precluded by the presence of a psychiatric disorder. This is important because several large longitudinal cohorts have provided compelling evidence that the age of onset of psychiatric symptoms is a crucial factor in determining the nature of these symptoms. These studies suggest that the later in life the onset of psychiatric symptomatology, the more likely these symptoms represent the early stages of a neurodegenerative process, precede dementia by 5–11 years [41–44], and have a higher progression rate than early onset psychiatric syndromes, which are themselves at heightened risk [13]. From a community cohort of 9,931 participants, the emergence of MBI was associated with decline in attention and working memory at 1 year [12]. In psychiatry and neurology specialty clinic samples, incidence of dementia was higher for MBI than other psychiatric disorders [13, 14]. This evidence suggests that chronic and recurrent psychiatric symptoms reflect a psychiatric disorder framed in the context of psychiatric conditions, are sometimes *neurodevelopmental* in origin, i.e., these conditions are not a consequence of later life neurodegenerative disease, supporting exclusion from our analysis. In contrast to this, late onset psychiatric symptoms may be prodromal or precursor to cognitive decline and dementia in some and are better framed in the context of *neurodegeneration*. The ISTAART-AA MBI criteria were developed with an appreciation of the difference between later life *de novo* behavioral changes, and psychiatric disease recurring in later life [9]. Indeed, MBI has been associated with amyloid, tau, and neurodegeneration, and is now harmonized with the biological understanding of AD [30].

**SCD**

SCD is also represented in Stage 2 AD of the NIA-AA research framework in which there is subjective or objective evidence of subtle decline, not meeting criteria for objective impairment. On the AD continuum, subjective complaints of cognitive impairment, with or without evidence of impairment on cognitive testing [45], would be considered evidence of subtle cognitive decline and attributable to the pathologic process [30]. Meta-analysis of large longitudinal cohorts has shown that SCD is associated with ORs of 6 of progression to MCI and 2 for progression to dementia over a mean of 4.8 years [6]. In a study of older adults with SCD, ascertained using a composite score of 3 rating scales, 26% were determined to be Aβ+[5]. However, significant inter-site variability in the association between SCD and abnormal cerebrospinal fluid amyloid levels has been attributed to different recruitment approaches and a lack of standardized case definitions and ascertainment [46]. There can be other contributors to subjective complaints of cognitive decline not limited to medical issues, stressors or even medications. Nonetheless, as with MBI, SCD reflects the index clinical manifestation of a neurodegenerative process for some.

**Intersection of MBI and SCD**

MBI and SCD intersect in some instances. For example, a study of SCD determined that worries about self-perceived functioning were associated with Aβ positivity, rather than subjective cognitive functioning itself [47]. Worries or concerns are included in the SCD plus criteria, proposed to increase specificity for detecting preclinical AD [3]. Worry is also a component of the MBI affective dysregulation domain, which includes emergent mood and anxiety symptoms. Mood symptoms and SCD have been shown to interact to predict dementia independent of their main effects [48], and similar results have been found examining persistent neuropsychiatric symptoms and MCI [15]. The approach to psychiatric symptomatology in SCD has generally utilized traditional constructs of personality (e.g., neuroticism) and psychiatric conditions [49–51]. However, a change in personality to greater neuroticism (which is a *neurodevelopmental* construct) can also be framed as the emergence of MBI affective dysregulation, if considered in a *neurodegenerative* frame of reference [49]. This intersection of MBI and SCD is consistent with both constructs being represented in NIA-AA stage 2 AD.

**NPI-Q informant report**

The source of information for MBI status in our study was the NPI-Q [36] completed by an informant.
The NPI-Q was developed to measure NPS in dementia, and the symptoms as described are relevant to an aging population with neurodegenerative disease. Informant reports have shown to be more reliable assessments of NPS in neurodegenerative disease to minimize the impact of anosognosia [52]. Coincidentally, in another study of SCD, confirmation of decline by an informant was the best predictor of worse cognitive performance and lower gray matter volumes [53]. Anosognosia is also important to consider in the assessment of SCD. The INSIGHT-PreAD study showed that patients with low cognitive awareness (reporting fewer difficulties than their relatives did) showed greater amyloid burden and lower cortical metabolism, compared to the high awareness group [54]. These findings suggest that self-report of symptoms alone, whether cognitive or behavioral, may not be adequate to capture early disease.

Clinical and research implications

Our data indicate that in cognitively normal older adults, the neurobehavioral axis of dementia risk represented by MBI, and neurocognitive axis of dementia risk represented by SCD, have complementary associations with the risk of progression to MCI and dementia. As operationalized in our study, MBI appears to be at least as strong a risk factor for progression to MCI or dementia as SCD and the two constructs have overlapping features. The combination of both MBI and SCD was associated with the highest risk (30.9% at 3 years), and this may have clinical utility by identifying a subset of individual at high risk of progression and reducing overmedicalization of risk markers that in isolation have low specificity.

In addition to screening for subjective and objective cognitive symptoms in older adults, incorporating MBI into clinical assessments may provide complementary information and better risk stratification [55, 56]. Not infrequently, dementia patients are first given a psychiatric diagnosis when presenting with a neuropsychiatric symptom, resulting in delays to treatment [57, 58]. Identifying MBI would prompt clinicians to consider neurocognitive disorders on the differential diagnosis, and flag patients who might benefit from imaging or further workup.

These findings also have clinical trial implications. Research and development costs are higher for AD than other therapy areas due to lower success rates and longer development times [2]. Despite the fact that changes in brain structure and function occur up to 20 years before gross memory impairment [59], screening for preclinical disease is expensive and inefficient. Leveraging the ease of measurement of MBI, in conjunction with SCD, could be an inexpensive and scalable method to select patients at highest risk for biomarker positivity and cognitive decline. For dementia prevention trials, combining MBI and SCD could increase yield and improve signal-to-noise ratios for clinical trial screening in order to identify an enriched group for assessment and workup. An associated reduction in screen failures could increase trial efficiency and decrease trial cost.

Limitations

The NACC participants are mostly white, highly educated volunteers seeking care and consultation at urban, university-based centers, and the finding may not generalize to other settings. Our choice of the CDR as the outcome measure was chosen for its clinical relevance, representing cognition-related daily function as a real-world outcome meaningful to patients, family members, and clinicians. However, this outcome does not provide as much detail on cognition as neuropsychological testing which could more accurately describe the performance of the four groups. For MBI case ascertainment, we used the NPI-Q [36] rather than the validated MBI-C [56, 60, 61] which was developed specifically to measure MBI. We used a validated algorithm to convert NPI-Q scores to MBI-C domains and required NPS at 2 consecutive visits to match the MBI criterion of symptom persistence. However, the cutoff of > 0 to define MBI+ may not provide optimum specificity and risks overestimating the MBI phenomenon. Although 44.5% of the participants had a dementia risk syndrome of either MBI or SCD (or both), 21.8% of these had cognitive and functional decline at 3 years (compared to 5.2% of participants with neither risk syndrome)—a substantial proportion, nonetheless. Additional research is needed to refine the group, balancing the risk of overmedicalization with the need to determine risk with sufficient sensitivity in order to not miss cases of preclinical disease; the MBI-C may help with this need. MBI criteria stipulate that symptoms are not better accounted for by life events. However, life context could not be determined using the data available and there may be a proportion of participants with reactive symptoms, even over the two-visit duration used to determine MBI status. Similarly, MBI criteria require symptoms to have an impact on interpersonal relationships, social func-
tioning and workplace performance. These data were not included in the analysis, and it is possible for some with mild symptoms to have minimal impact in those domains.

CONCLUSION

In summary, we have demonstrated that MBI, a neurobehavioral syndrome, is an important predictor of incident cognitive and functional decline at 3 years in cognitively normal subjects, supporting the use of MBI as a powerful risk assessment tool. Our findings suggest that MBI is at least as useful as SCD in assessing risk for incident cognitive decline and dementia, and that the two constructs are likely complementary. Assessment of the neurobehavioral and neurocognitive axes at the same time are required in cognitively normal individuals to better define their risk.

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