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RESEARCH ARTICLE

Mild behavioral impairment in the general population aged 55+ and its association with incident dementia

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Abstract

This study aimed to investigate the dementia risk associated with mild behavioral impairment (MBI) and its domains in older community-dwelling individuals. A total 4803 community-dwelling individuals aged over 55 years were followed for 4.5 years (ZARADEMP study). MBI was assessed according to the International Society to Advance Alzheimer's Research and Treatment (ISTAART) diagnostic criteria using the Geriatric Mental State (GMS). Odds ratios (OR) for incident dementia and Alzheimer's disease (AD) were determined using logistic regression models adjusted for potential confounders (such as age, disability, or vascular disease). In cognitively normal individuals, decreased motivation was the only MBI domain that was associated with an increased risk of all-cause dementia (OR: 2.30 [95% confidence interval {CI}: 1.16-4.61]) in multivariable analyses, although the increase in the risk of AD was not statistically significant. Our findings suggest that decreased motivation may be a phenotypic marker for individuals at risk of dementia. Further research is required to evaluate the association between MBI domains and different types of dementia.

KEYWORDS
aging, dementia, mild behavioral impairment, neuropsychiatric symptoms, non-cognitive symptoms

1 | INTRODUCTION

In 2017, the International Society to Advance Alzheimer's Research and Treatment (ISTAART) identified late-life onset neuropsychiatric symptoms (NPS) as an "at-risk" state, termed "mild behavioral impairment" (MBI).[1]

A relatively high prevalence of MBI is reported in the general population.[2,3] Moreover, MBI increases as cognitive impairment progresses.[2,3] The frequency of MBI in cognitively normal (CN) individuals is more than 25%, particularly in the domains of affective dysregulation and impulse dyscontrol.[2,3] Over the past 3 years, the longitudinal association between MBI and cognitive decline[4–6] and dementia[6–8] has been evidenced. However, MBI dimensions have different prognostic implications.[7–9] Gill et al.[7] reported an association between impulse dyscontrol and affective dysregulation in the diagnosis of Alzheimer's disease (AD). Yoon et al.[9] investigated individuals with mild cognitive impairment (MCI) and found that there is an increased risk of progression to AD in those with MBI including multiple domain symptoms, specifically affective dysregulation, impulse dyscontrol, and decreased motivation. In the largest sample to date, including only CN individuals, Ruthirakuhan et al.[8] found that there is an increased risk of AD in individuals with symptoms in any MBI domain, with abnormal perception and thoughts being associated with the greatest risk, followed by social inappropriateness, impulse dyscontrol, decreased motivation, and affective dysregulation. Vellone et al.[10] found a markedly increased risk of dementia in individuals with apathy, particularly in individuals with CN. However, most longitudinal studies recruited participants from clinical settings, who may not represent the general population.[8] Only one study was based on a community sample of volunteers; however, it did not specifically study dementia risk or the prognostic value of individual MBI domains.[4]

The MBI checklist (MBI-C), published in 2017,[1] is the only validated tool to assess MBI in predementia populations, and it has only recently been incorporated into studies and cohorts.[4,10] The Neuropsychiatric Inventory Questionnaire (NPI-Q)[11] is the most commonly used tool to define MBI.[3] Although proxy measures using available instruments may not fully capture some MBI symptoms,[8] they provide an important method to retrospectively assess MBI in existing datasets. However, the NPI-Q was designed to assess NPS in patients with dementia through an informant report and was designed for use in routine clinical practice.[11] The brief version of the Geriatric Mental State Survey (GMS-B), a tool developed specifically for epidemiological research,[12,13] might be particularly relevant to study community samples. The GMS-B is a comprehensive clinical interview that explores prevalent NPS among elderly individuals in the general population,[12,13] including cognitive and a large range of affective symptoms (depression, tearfulness, pessimism, guilt, irritability, worry, interest, enjoyment, etc.). Widely validated globally, the GMS-B demonstrates high reliability, enabling comparisons across epidemiological studies.[13]

We reported a specific association between negative-type symptoms assessed using the GMS-B (such as slowness and restriction of activity) and dementia.[14] We expect that the dimensions assessing MBI symptoms such as decreased motivation, may have a particular weight in determining the potentially increased risk of dementia in the general population.

Hence, the present study aimed to:

Compare the prevalence of MBI (and specific MBI domains) using the GMS-B in a representative sample of community-dwelling older individuals with the results of studies using other methods for MBI assessment in similar populations.

Determine whether the frequencies of MBI and specific MBI domains were higher in cognitively impaired, nondemented (CI-ND) individuals than in CN individuals.

Test the hypotheses that (a) MBI assessed by the GMS-B increases the probability of developing dementia and AD in CN individuals in the general population, and (b) MBI domains may be differentially associated with this increased probability, particularly the decreased motivation dimension.

RESEARCH IN CONTEXT

1. **Systematic review**: There is growing evidence for a longitudinal association between mild behavioral impairment (MBI) and dementia. Most studies recruited samples from clinical settings and used the Neuropsychiatric Inventory to assess MBI, a test designed to assess neuropsychiatric symptoms in dementia populations. Relevant publications in this field have also been cited.
2. **Interpretation**: Our findings suggest that the MBI domain decreased motivation, as assessed by Geriatric Mental State B, an interview specifically for older individuals of the community, may help detect subjects at-risk for dementia in this population, specifically non-Alzheimer's dementia.
3. **Future directions**: Our manuscript supports the relevance of studying MBI domains and the risk of different types of dementia separately. Further studies should elucidate the pathway associations between decreased motivation and dementia and help develop early treatment targets for at-risk populations.

2 | METHODS

2.1 | Sample

We used data from the Zaragoza Dementia and Depression (ZARADEMP) project, a longitudinal study that documented the incidence and risk factors of dementia in adults aged ≥55 years.[15] The sample was randomly collected from the official Spanish Census and stratified according to age and sex. The refusal rate was 20.5%, and 4803 individuals finally participated at baseline (starting in 1994). For this work, and following MBI ISTAART criteria, "cases" of dementia, depression, and anxiety (see criteria below) were excluded, so the

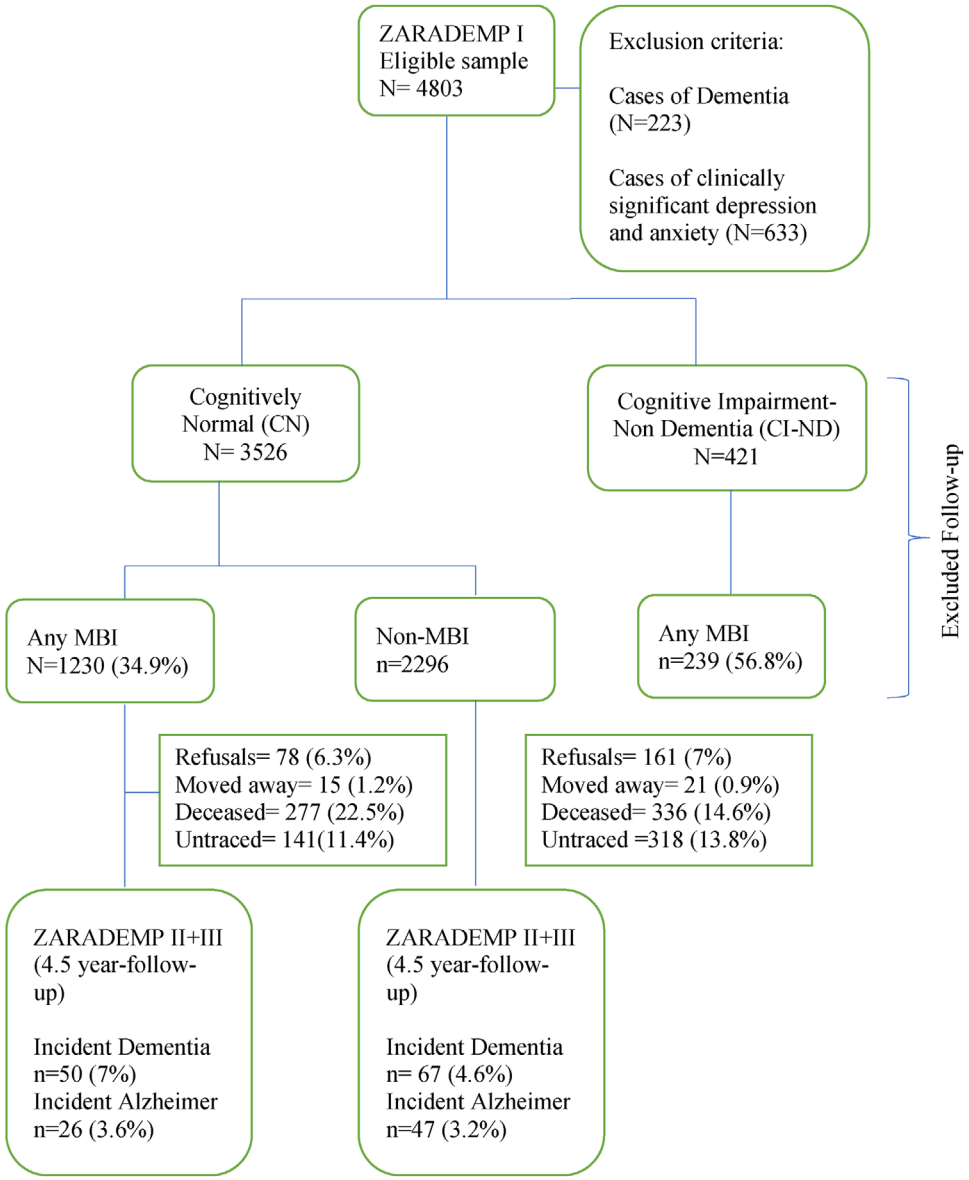

FIGURE 1 Study flow chart.

final baseline sample included 3947 individuals. For the longitudinal analysis, we included only CN individuals at baseline ($n = 3526$).

Figure 1 illustrates a flow diagram of the ZARADEMP Project and the present study.

2.2 | Instruments

Validated Spanish versions of the Mini-Mental Status Examination (MMSE) (scored from 0 to 30),[16] GMS-B, Automated Geriatric Examination for Computer-Assisted Taxonomy (AGECAT),[17] History and Etiology Schedule (HAS),[18] Katz's Index for Basic Activities of Daily Living (bADL),[19] Lawton and Brody scale for instrumental activities (iADL),[20] and European Studies of Dementia (EURODEM) risk factors questionnaire.[21]

The GMS is a semistructured standardized clinical interview for older adults. GMS-B includes a subset of 12 items that contribute to the diagnosis of cognitive deficits, including minor disturbances.[12] The GMS-B provides a "threshold global score" that discriminates between "noncases" (0), "subcases" (0/1), and "cases" (1/2) of dementia.[14] The GMS is supported by AGECAT, an algorithm that synthesizes clinical profiles into diagnostic "clusters"[13] This tool uses standardized levels of illness for case-finding at baseline and follow-up.[15] Confidence levels ≥3 (named "cases") demonstrated good sensitivity and specificity in identifying individuals requiring clinical intervention in the general population.[22] The GMS has been validated against most major diagnostic systems for depression and dementia in community studies and permits the application of the latest DSM algorithms.[13] Furthermore, the GMS is supported by the use of the HAS, a standardized interview given to an informant to clar-

ify the psychiatric diagnosis when appropriate after the GMS is administered.[18]

2.3 | MBI assessment and diagnosis

MBI was assessed according to the ISTAART research diagnostic criteria,[1] except for the duration and new-onset criteria. We utilized the GMS-B items according to the MBI-C.[1] Table 1 presents the transformation matrix of the GMS-B items used to approximate whether the participants scored the MBI-C items. Matching was initially performed by the main author following previous operational definitions of non-cognitive symptoms in the same sample[14] and was reviewed by two other researchers to reach a full agreement. We used the duration criterion of the GMS-B, which assesses symptoms over the previous month. In addition to the participants' responses, the GMS-B includes observational items and judgments rated by the interviewer. In this study, we also used informant-reported changes in personality using the HAS when available.

To meet the criteria for a specific MBI domain, participants were required to present one or more GMS symptom items constituting this domain. Participants met the overall criteria for MBI if at least one of the five MBI domains was present.

As diagnosis of MBI is precluded by a formal psychiatric diagnosis,[1] "cases" of depression and anxiety identified according to GMS-AGECAT criteria were excluded.

2.4 | Cognitive status at baseline and incident dementia

A two-phase screening procedure was implemented at baseline (Wave I of ZARADEMP Study). Participants were identified as "probable cases" of dementia based on the GMS-B threshold global (1/2) and MMSE standard cutoff (<24) scores, showing adequate negative predictive value,[12] so that participants classified as nondemented had a higher likelihood of being cognitively healthy. The diagnosis of dementia was confirmed by a research psychiatrist using standardized methods.[15]

Individuals with borderline scores (GMS threshold global score 0/1) were classified as "subcases" of "dementia" or CI-ND group. Some of them could be incipient dementia cases, and incidence results could be impacted; therefore, these cases were excluded from the follow-up in the ZARADEMP study.[15]

At follow-up (Waves II and III of the ZARADEMP study), a similar two-phase screening procedure was performed after a mean of 2 and 4.5 years, respectively. Subsequently, a panel of psychiatrists recorded the diagnosis of dementia and AD using the DSM-IV criteria,[23] whereas the validity of this diagnostic process was demonstrated.[15] To document the accuracy of the panel, some of the detected cases were subjected to a hospital diagnostic workup. Agreement on the diagnosis of dementia between community and hospital assessments was reached in 95.8% of cases.

2.5 | Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics version 26. Prevalence estimates for the MBI and MBI domains at baseline were reported for the study groups (CN and CI-ND). The χ^2 test and analysis of variance were used to compare the prevalence of MBI between groups and other categorical variables and independent samples t-test for continuous variables. Statistical significance was set at $P < 0.05$.

Variables that showed significant differences between the CI-ND and CN groups were compared to determine the differences in the presence or absence of MBI symptoms. Those with statistically significant differences ($P < 0.01$) and/or those consistently recognized as risk factors for dementia, such as low educational level[24] and vascular disease,[25] were included as potential confounders in the multivariate logistic regression models (see below).

Bivariate and multivariable logistic regression models were used to estimate the probability of developing dementia at the 4.5-year follow-up in CN individuals with MBI. Bivariate models included MBI, each MBI domain separately, and potential confounders as independent variables, and incident dementia and AD as outcome variables. The multivariate models included age, sex, educational level, cognitive status at baseline (MMSE score), functional disability (disability for at least one bADL or iADL), and vascular diseases (angina and/or myocardial infarction and/or stroke) as potential confounders.

2.6 | Ethical considerations

The Ethics Committee of the University of Zaragoza and Fondo de Investigación Sanitaria (FIS) approved this study according to Spanish Law, and the principles of written informed consent, privacy, and confidentiality were maintained throughout the project.

3 | RESULTS

3.1 | MBI prevalence and associated variables at baseline

Table 2 shows characteristics of the baseline sample and the prevalence of MBI by cognitive status. Compared with the CN group, individuals with CI-ND were older, more frequently women, had a lower education level, lower MMSE score, presented more frequent disability, and had a higher prevalence of vascular disease, with these differences being statistically significant. They also had a significantly higher prevalence of MBI (56.8% vs. 34.9%) and most MBI domains, except for social inappropriateness, which was infrequent (1.2%) in both groups. Among the CI-ND, the most common MBI domains included decreased motivation (35.2%), affective dysregulation (31.6%), and impulse dyscontrol (19%). Abnormal perception and thoughts were observed in 7.4% of CI-ND individuals. In the CN group, the most common MBI domains included affective dysregulation (23.8%), decreased motivation (10.6%), and

TABLE 1 Diagnostic criteria of MBI used in the study.

ISTAART		
MBI domain	**GMS- #HAS items**	**MBI-C[a] items**
Decreased motivation	Decreased interest for regular activities.	Has the person lost interest in friends, family, or home activities?
	Observed slowing and/or lack of spontaneous conversation.	Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?
	Decreased of participation on regular activities.	Has the person lost motivation to act on her/his obligations or interests?
	#Change on personality reported by informant: lack of interest or affection.	Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?
	No longer care or enjoy about anything.	Does she/he no longer care about anything?
Affective dysregulation	Depressed mood or tearfulness.	Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?
	No able to enjoy of pleasurable experiences.	Has the person become less able to experience pleasure?
	Pesimism about future.	Has the person become discouraged about their future or feel that she/he is a failure?
	Trend to self-blaim or to feel useless.	Does the person view herself/himself as a burden to family?
	Worry about almost everything, including routine events.	Has the person become more anxious or worried about things that are routine (e.g., events, visits, etc.)?
	Inability to relax or symptoms of panic.	Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?
Impulsive dyscontrol	Irritability, almost every day, for more than 2 weeks or #change of personality (more irritable) reported by informant.	Has the person become agitated, aggressive, irritable, or temperamental?
	Observed lack of cooperation and argumentative behavior.	Has she/he become unreasonably or uncharacteristically argumentative?
	Observed repetitive behaviors or speech.	Has the person developed simple repetitive behaviors or compulsions?
Social inappropriateness	Observed loss of appropriate social behavior (deliberately throw or crack something, obscene words or gestures, bland or inappropriate jokes or comments).	Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?
		Does the person seem to lack the social judgment she/he previously had about what to say or how to behave in public or private?
Abnormal perception or though content	Observed suspiciousness or #change of personality reported by informant (more suspicious and/or blame others of mistreatment or robbery).	Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?
		Has the person developed suspiciousness about the intentions or motives of other people?
	Any abnormal perception (visual, auditive or sensitive) or other psychotic symptom.	Does the person describe hearing voices or does she/he talk to imaginary people or "spirits"?
		Does the person report or complain about, or act as if seeing things (e.g., people, animals or insects) that are not there, that is, that are imaginary to others?

Abbreviations: GMS, Geriatric Mental State Survey; ISAART, International Society to Advance Alzheimer's Research and Treatment; HAS, History and Etiology Schedule; MBI, mild behavioral impairment; MBI-C, MBI checklist.
[a]Ismail Z, 2016. MBItest.org.

impulse dyscontrol (5.3%), whereas the least common symptom was abnormal perception and thoughts (2.1%).

Table 3 shows characteristics of the CN group according to behavioral (MBI) status. Individuals with MBI, compared with those without MBI, were older and more frequently women, had a lower education level, lower MMSE score, more frequent disability, and higher prevalence of vascular disease, with these differences being statistically significant. Among CN participants, individuals with MBI symptoms showed a similar demographic and clinical profile to CI-ND participants. In both cases, a less favorable profile than their respective reference groups, non-MBI (Table 3) and CN individuals was observed (Table 2).

TABLE 2 Baseline characteristics of the participants and prevalence of MBI and its domains by cognitive status.

Parameter	Overall sample ($n = 3947$)		Cognitive normal (CN) ($n = 3526$)		Cognitive impairment-no dementia (CI-ND) ($n = 421$)		Test statistic	
	Mean	SD	Mean	SD	Mean	SD	T-test	*p*-Value
Age (years)	72.8	9.5	**71.9**	**9.1**	**79.8**	**9.5**	-16.01	<0.001
MMSE-30	26.5	3.7	**27.3**	**2.5**	**19.6**	**4.7**	33.3	<0.001
	n	%	*n*	%	*n*	%	χ^2	
Women	2103	53.3	**1813**	**51.4**	**290**	**68.9**	46.01	<0.001
Education (vs. illiterate)								
Primary school	2864	72.6	**2598**	**74.3**	**266**	**63.6**	192	<0.001
Higher school	649	16.4	**632**	**18.1**	**17**	**4.1**	191.8	<0.001
Any disability	352	8.9	**191**	**5.4**	**161**	**38.2**	497.8	<0.001
Hypertension	2456	62.2	2190	67.7	266	70.4	1.13	0.29
Diabetes	472	12	417	11.9	55	11.7	0.58	0.43
Vascular disease	448	11.4	**381**	**11.2**	**67**	**16.8**	10.7	<0.001
MBI	1469	37.2	**1230**	**34.9**	**239**	**56.8**	77.1	<0.001
Decreased motivation	523	13.3	**375**	**10.6**	**148**	**35.2**	196.7	<0.001
Affect dysregulation	971	24.6	**838**	**23.8**	**133**	**31.6**	12.4	<0.001
Impulse dyscontrol	266	6.7	**188**	**5.3**	**78**	**19**	108.4	<0.001
Social inappropriateness	48	1.2	43	1.2	5	1.2	0.00	1.00
Abnormal perception or thought content	102	2.6	**72**	**2.1**	**30**	**7.4**	40.4	<0.001

Note: Statistically significant differences ($p < 0.05$) between groups are in bold.
Abbreviations: MBI: mild behavioral impairment; MMSE, Mini-Mental State Examination; SD: standard deviation.

TABLE 3 Characteristics of cognitively normal (CN) participants at baseline by behavioral status.

Cognitive normal (CN)	Overall sample ($n = 3526$)		Non-MBI ($n = 2296$)		MBI ($n = 1230$)		Test statistic	
	Mean	SD	Mean	SD	Mean	SD	*T*-test	*p*-Value
Age (years)	71.9	9.1	**71.1**	**8.7**	**73.5**	**9.7**	-7.6	<0.001
MMSE-30	27.3	2.5	**27.4**	**2.5**	**27.0**	**2.5**	5.04	<0.001
	n	%	*n*	%	*n*	%	χ^2	
Women	1813	51.4	**1070**	**46.6**	**743**	**60.4**	61.1	<0.001
Education (vs. illiterate)								
Primary school	2598	73.3	**1693**	**73.7**	**905**	**7**	5.7	0.019
Higher school	632	17.9	**430**	**18.9**	**202**	**16.6**	8.6	<0.001
Any disability	191	5.4	**59**	**2.6**	**132**	**10.7**	103	<0.001
Vascular disease	381	10.8	**230**	**10.4**	**151**	**12.7**	4.15	0.046

Note: Statistically significant differences ($p < 0.05$) between groups are in bold.
Abbreviations: MBI: mild behavioral impairment; SD: standard deviation.

3.2 | Incident dementia at follow-up

The proportion of CN individuals with MBI fulfilling the diagnostic criteria for all-cause dementia at follow-up (50 cases, 7.0%) was significantly higher than in those with no MBI symptoms (67 cases, 4.6%) ($\chi^2 = 5.3$; $P = 0.02$). However, the proportion of CN individuals with MBI fulfilling the diagnostic criteria for AD at follow-up (26 cases, 3.6%) was similar to that of individuals with no MBI symptoms (47 cases, 3.2%) ($\chi^2 = 0.23$; $P = 0.61$).

Incident cases of dementia for each MBI domain (compared with individuals without these symptoms) were: 31 (26.5%; $\chi^2 = 49.6$; $P < 0.001$) in individuals with decreased motivation; 26 (5.1%;

TABLE 4 Association of MBI and its domains with incident dementia and Alzheimer's dementia.

	All-cause dementia		Alzheimer's dementia	
a. Logistic regression bivariate	**OR (CI 95%)**	***p*-Value**	**OR (CI 95%)**	***p*-Value**
MBI	**1.55 (1.06-2.27)**	**0.022**	1.13 (0.64-1.84)	0.628
Decreased motivation	**4.34 (2.79-6.75)**	**<0.001**	**2.62 (1.43-4.78)**	**0.002**
Affect dysregulation	0.93 (0.59-1.46)	0.756	0.70 (0.38-1.29)	0.253
Impulse dyscontrol	1.58 (0.78-3.22)	0.203	1.37 (0.54-3.48)	0.504
Social inappropriateness	0 (0)	0.998	0 (0)	0.998
Abnormal perception and thoughts	1.59 (0.48-5.24)	0.450	2.63 (0.79-8.77)	0.116
Age (years)	**1.21 (1.17-1.24)**	**<0.001**	**1.24 (1.19-1.29)**	**<0.001**
Sex (women)	1.25 (0.86-1.82)	0.250	**1.80 (1.10-2.95)**	**0.019**
Education (vs. illiterate)				
Primary school	**0.34 (0.20-0.57)**	**<0.001**	**0.29 (0.16-0.55)**	**<0.001**
Higher school	**0.15 (0.07-0.33)**	**<0.001**	**0.17 (0.07-0.41)**	**<0.001**
MMSE-30	**0.68 (0.63-0.72)**	**<0.001**	**0.67 (0.62-0.73)**	**<0.001**
Any disability	**16.7 (9.86-28.09)**	**<0.001**	**9.82 (5.23-18.41)**	**<0.001**
Vascular disease	**1.95 (1.16-3.27)**	**0.011**	1.30 (0.64-2.66)	0.468
	All-cause dementia		**Alzheimer's dementia**	
Logistic regression multivariable[a]	**OR (CI 95%)**	***p*-Value**	**OR (CI 95%)**	***p*-Value**
Mild behavioral impairment	1.01 (0.63-1.61)	0.959	1.39 (0.78-2.45)	0.268
Decreased motivation	**1.87 (1.06-3.31)**	**0.032**	1.04 (0.49-2.19)	0.920
Affect dysregulation	1.16 (0.68-2.01)	0.165	1.53 (0.75-3.10)	0.236
Impulse dyscontrol	1.56 (0.57-4.31)	0.386	1.84 (0.53-6.40)	0.339
Social inappropriateness	n/a		n/a	
Abnormal perception and thoughts	3.00 (0.50-17.86)	0.227	1.12 (0.20-6.33)	0.898

Abbreviation: CI, cognitive impairment; MBI: mild behavioral impairment; MMSE; Mini-Mental State Examination; OR, odds ratio.
[a]Variables included in multivariable logistic regression models are age, sex, educational level, cognitive (MMSE score) and functional status at baseline, and vascular disease.
Bold values represent statistically significant results.

χ^2 = 0.10; P = 0.823) in individuals with affective dysregulation; 9 (8%; χ^2 = 1.65; P = 0.195) in individuals with impulse dyscontrol; zero in individuals with social inappropriateness; and 3 (8.1%; χ^2 = 0.58; 0.314) in individuals with abnormal perception and thoughts. For incident AD, the figures were: 14 (7.4%; χ^2 = 10.5; P = 0.004) individuals with decreased motivation, 13 (2.5%; χ^2 = 1.32; P = 0.324) individuals with affective dysregulation, 5 (6.8%; χ^2 = 0.45; P = 0.422) individuals with impulse dyscontrol, and 3 (χ^2 = 2.67; P = 0.13) individuals with abnormal perception and thoughts.

In bivariate analysis, the probability of developing all-cause dementia at 4.5 years was increased for individuals with MBI (OR: 1.55, 95%CI: 1.06-2.27); however, significance was not confirmed in the multivariable model. The probability of developing AD did not significantly increase in participants with MBI (Table 4).

In bivariate models, decreased motivation significantly increased the probability of developing dementia at the 4.5-year follow-up for all-cause dementia (OR: 4.34, 95%CI: 2.79-6.75) and AD (OR: 2.62, 95%CI: 1.43-4.78). However, considering all potential confounders, the association between decreased motivation and all-cause dementia remained significant (OR: 1.87, 95%CI: 1.06-3.31), but not for AD. No significant differences were found in other MBI domains (Table 4).

4 | DISCUSSION

Using the GMS-B as an assessment tool, the prevalence of MBI and specific MBI domains in the general population aged > 55 years was considerable. We found a significant increase in incident dementia, but not in AD, in participants with MBI, although significance was not confirmed in the multivariable analysis. Conversely, the increased incidence of dementia associated with decreased motivation remained significant after controlling for potential confounders and was almost double compared to CN individuals with no related symptoms.

The prevalence of MBI documented in this study confirms the relevance of this clinical problem.[1] Using the GMS-B, we found an intermediate prevalence of MBI (37.2%) compared with other studies of community samples assessing MBI using different approaches.[2,26]

Our results also support previous findings[2,3] reporting a significantly higher prevalence of MBI in individuals with cognitive impairment.

As patients with NPS are more likely to seek treatment,[27] this considerable prevalence of several MBI domains suggests specific clinical needs.[2,5,28] We found a prevalence for the different MBI domains that lies within the interval coefficients of pooled prevalence reported in the meta-analysis by Pan et al.,[3] except for impulse dyscontrol in the CN and social inappropriateness in both cognitive groups, representing a possible limitation of the GMS-B in detecting symptoms in these domains. In fact, other community studies using either the NPI[2] or MBI-C[26] found frequencies of 16%[2] to 38%[26] for impulse dyscontrol and 5%[2] to 12%[26] for social inappropriateness in CN older adults. Our results suggest that the GMS-B can identify the MBI domains affective dysregulation, decreased motivation, and abnormal perceptions and thoughts in community-dwelling older adults. However, sensitivity in identifying impulse dyscontrol and social inappropriateness is low. The GMS-B does not capture symptoms defined in the MBI impulsive dyscontrol domain, such as impulsive or disinhibited behaviors and changes in oral intake; only one observational item refers to inappropriate social behavior and no evaluation of empathy. A lack of insight could also have affected prevalence rates[26] compared to studies using the NPI, which obtains information from a caregiver. We attempted to overcome this limitation by including observational items from the GMS and informant-reported changes from the HAS. Differences in prevalence of these MBI domains may also result from cohort characteristics. Further studies validating the use of the GMS-B to distinguish MBI in other community samples are required.

Several studies explored longitudinal outcomes of MBI use. Creese et al.[4] reported a decline in attention and working memory scores at 1 year, while Ismail et al.[5] found that the MBI could be a predictor of cognitive and functional decline at 3 years. Furthermore, using machine learning methods, Gill et al.[7] reported that MBI total scores, along with left hippocampal volume, had acceptable predictive values for dementia diagnosis.[7] Kan et al.[6] found that MBI increased the incident dementia risk by 2.56-fold at 4 years, while Ruthirakuhan et al.[8] found that MBI significantly predicted progression to AD. In the present study, we did not observe a significant increase in the risk of dementia in participants with MBI after controlling for potential confounders. Unfavorable demographic and clinical factors such as low educational level and vascular disease, recognized as independent risk factors for dementia,[24,25] were found to be more prevalent in individuals with MBI at baseline in our study. This might have influenced the association between MBI and dementia in the bivariate analysis. Additionally, previous studies using samples from clinical settings showed higher incidences of dementia[5,6] and AD[8] than did our population-based study, which may confer an advantage to the previous studies detecting significant results.

To the best of our knowledge, this is the first longitudinal study based on a random sample of the general population using the GMS-B to assess MBI domains. Decreased motivation was the only MBI domain associated with incident dementia. This domain reflects the apathy syndrome,[1] which may represent a useful phenotype in predictive risk models for dementia in different clinical samples.[28] Most studies were based on clinical samples from patients with MCI;[29,30] however, a recent meta-analysis[31] including studies on CN populations reported that apathy doubles the risk of progression to dementia, in line with our results. Moreover, a recent study[10] reported a more than five-fold increased risk of dementia in CN individuals with apathy according to strict MBI criteria (considering new-onset symptoms persisting for more than 6 months). As Mortby et al.[32] suggested in their recent review, the incorporation of MBI-apathy into observational and interventional studies will help understand its role as a dementia prodrome.

Nevertheless, Ruthirakutan et al.[8] reported a significant increase in the risk of AD in each MBI domain. Although their sample was larger, it was recruited from clinical settings and individuals with depression or anxiety were not excluded, potentially leading to an overestimation of MBI frequency and the associated AD risk. We previously reported that individuals with severe depression[33] and clinically significant anxiety[34] have a four-fold increased risk of developing AD. Further longitudinal studies are needed to evaluate the independent associations between each MBI domain and the different types of dementia.

The observation that decreased motivation was associated with all-cause dementia but not AD in this study highlights its importance in non-AD dementia. Furthermore, Vellone et al.[10] reported that participants with apathy who progressed to dementia at the 10-year follow-up were more often non-AD cases than individuals without NPS at baseline. The under-and misdiagnosis of non-AD-type dementia is a key issue,[35] while decreased motivation in older adults with CN may help identify individuals at risk. Decreased motivation may reflect dysfunction of the prefrontal cortex, basal ganglia, and/or frontosubcortical connectivity,[28] occurring in many forms of non-AD dementia.[36] This may be relevant in the research for neurobiological correlates of apathy and identification of treatment targets.[29] Moreover, MBI symptoms are linked with known AD biomarkers[37,38] and AD risk genes,[39] such as apolipoprotein E (*APOE*).[8,10] However, further studies are needed to explore their associations with non-AD biomarkers.[37]

The potential impact of treatments targeting decreased motivation needs to be determined. Currently, there are no established treatments for apathy. However, nonpharmacological interventions, specifically therapeutic activities adapted for each individual, have shown promising results[32]

4.1 | Strengths and limitations

This study was conducted in a large, community-dwelling representative population, whereas previous studies recruited participants from specialist memory clinics.[8,10] Moreover, we studied the risk of overall dementia and AD. Our study is the first to use the GMS-B, a full diagnostic interview specifically designed and validated for the assessment of older individuals in the community. The GMS-B covers a large range of symptoms included in the decreased motivation domain, such as a decrease in spontaneous conversation and participation in regular activities, lack of enjoyment, and carelessness.

A limitation of our study, as in other studies utilizing a single time-point NPI measure,[4,8,9] is that the GMS-B assesses symptoms over the previous month; therefore, symptoms persisting for over 6 months, required by the MBI criteria,[1] cannot be assessed, while some authors found an increased dementia risk for persistent compared to transient NPS.[6,10] Moreover, we did not search for a history of psychiatric symptoms in adulthood; therefore, we could not confirm the criteria for the emergence of symptoms in late life.[1] Our method may have overestimated the prevalence of MBI[3]; however, we found a lower prevalence of MBI and all MBI domains than authors who used the MBI-C assessment.[26] Although we attempted to find a proxy for each MBI-C item in the GMS-B, some items were not necessarily equal, whereas others were not evaluated by the GMS-B, mostly in the impulse dysregulation and social inappropriateness domains. These limitations may reduce the specificity of the symptoms and magnitude of their association with the dementia risk.[6,10] We used the cutoff of one to define the presence of MBI and MBI domains.[2,3,26] While this cutoff point is supported to some extent by the positive results of longitudinal studies,[5] we cannot exclude that a higher cutoff value for predicting dementia and AD would be superior. We did not evaluate the effect of complex MBI (i.e., individuals with multiple MBI domain symptoms), which could increase the risk of progression to dementia relative to those with symptoms in a single domain.[9] Unlike other studies,[6,7,9,10,30] we were unable to analyze the association between MBI scores and incident dementia in cognitively impaired individuals. As the ZARADEMP study was designed to document incident cases of dementia, cognitively impaired individuals at baseline were excluded from follow-up.

5 | CONCLUSION

This study confirmed the relatively high prevalence of MBI and MBI domains in the general population using a novel assessment approach, the GMS-B, and established the relevance of this problem from public health and clinical perspectives.

Our results indicate that MBI domains may be differentially associated with dementia probability. Decreased motivation was the only domain associated with double probability of developing incident dementia, but not AD. Therefore, decreased motivation may be considered an early marker of individuals at-risk of developing dementia in the general population. Hence, decreased motivation should receive special emphasis in MBI diagnosis and further studies of its biological basis and potential applications are warranted.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants provided written informed consent. Privacy and confidentiality were maintained throughout the study.

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REFERENCES

1. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The mild behavioral impairment checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. *J Alzheimers Dis*. 2017;56:929-938. doi:10.3233/JAD-160979
2. Mortby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. *Int Psychogeriatr*. 2018;30:221-232. doi:10.1017/S1041610217001909
3. Pan Y, Shea Y-F, Ismail Z, et al. Prevalence of mild behavioural impairment domains: a meta-analysis. *Psychogeriatrics*. 2022;22:84-98. doi:10.1111/psyg.12782
4. Creese B, Brooker H, Ismail Z, et al. Mild behavioral impairment as a marker of cognitive decline in cognitively normal older adults. *Am J Geriatr Psychiatry*. 2019;27:823-834. doi:10.1016/j.jagp.2019.01.215
5. Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE. Mild behavioral impairment and subjective cognitive decline predict cognitive and functional decline. *J Alzheimers Dis*. 2021;80:459-469. doi:10.3233/JAD-201184
6. Kan CN, Cano J, Zhao X, Ismail Z, Chen CL-H, Xu X. Prevalence, clinical correlates, cognitive trajectories, and dementia risk associated with mild behavioral impairment in Asians. *J Clin Psychiatry*. 2022;83:21m14105. doi:10.4088/JCP.21m14105
7. Gill S, Mouches P, Hu S, et al. Using machine learning to predict dementia from neuropsychiatric symptom and neuroimaging data. *J Alzheimer Dis*. 2020;75:277-288. doi:10.3233/JAD-191169
8. Ruthirakuhan M, Ismail Z, Herrmann N, Gallagher D, Lanctôt KL. Mild behavioral impairment is associated with progression to Alzheimer's disease: a clinicopathological study. *Alzheimers Dement*. 2022;18:2199-2208. doi:10.1002/alz.12519
9. Yoon EJ, Lee J-Y, Kwak S, Kim YK. Mild behavioral impairment linked to progression to Alzheimer's disease and cortical thinning in amnestic mild cognitive impairment. *Front Aging Neurosci*. 2022;14:1051621. doi:10.3389/fnagi.2022.1051621

10. Vellone D, Ghahremani M, Goodarzi Z, Forkert ND, Smith EE, Ismail Z. Apathy and *APOE* in mild behavioral impairment, and risk for incident dementia. *Alzheimers Dement*. 2022;8:e12370. doi:10.1002/trc2.12370
11. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12:233-239. doi:10.1176/jnp.12.2.233
12. Lobo A, Saz P, Dia JL. The AGECAT "organic" section as a screening instrument for minor cognitive deficits. *Psychiatr J Univ Ott*. 1990;15:212-215.
13. Copeland JRM, Prince M, Wilson KCM, Dewey ME, Payne J, Gurland B. The geriatric mental state examination in the 21st century. *Int J Geriatr Psychiatry*. 2002;17:729-732. doi:10.1002/gps.667
14. Lobo A, López-Antón R, de-la-Cámara C, et al. Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type. *Neurotox Res*. 2008;14:263-272. doi:10.1007/BF03033815
15. Lobo A, Saz P, Marcos G, et al. The ZARADEMP Project on the incidence, prevalence and risk factors of dementia (and depression) in the elderly community: II. Methods and first results. *Eur J Psychiatr*. 2005;19:40-54.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198. doi:10.1016/0022-3956(75)90026-6
17. Copeland JR, Dewey ME, Griffiths-Jones HM. A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. *Psychol Med*. 1986;16:89-99. doi:10.1017/s0033291700057779
18. Dewey ME, Copeland JR. Diagnosis of dementia from the history and aetiology schedule. *Int J Geriatr Psychiatry*. 2001;16:912-917. doi:10.1002/gps.446
19. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. *JAMA*. 1963;185:914-919. doi:10.1001/jama.1963.03060120024016
20. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179-186.
21. Launer LJ, Brayne C, Breteler MM. Epidemiologic approach to the study of dementing diseases: a nested case-control study in European incidence studies of dementia. *Neuroepidemiology*. 1992;11(1):114-118. doi:10.1159/000111005 Suppl
22. Schaub RT, Linden M, Copeland JRM. A comparison of GMS-A/AGECAT, DSM-III-R for dementia and depression, including subthreshold depression (SD)–results from the Berlin Aging Study (BASE). *Int J Geriatr Psychiatry*. 2003;18:109-117. doi:10.1002/gps.799
23. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV*. American Psychiatric Association; 1994.
24. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390:2673-2734. doi:10.1016/S0140-6736(17)31363-6
25. Kling MA, Trojanowski JQ, Wolk DA, Lee VMY, Arnold SE. Vascular disease and dementias: paradigm shifts to drive research in new directions. *Alzheimers Dement*. 2013;9:76-92. doi:10.1016/j.jalz.2012.02.007
26. Creese B, Griffiths A, Brooker H, et al. Profile of mild behavioral impairment and factor structure of the Mild Behavioral Impairment Checklist in cognitively normal older adults. *Int Psychogeriatr*. 2020;32:705-717. doi:10.1017/S1041610219001200
27. Matsuoka T, Ismail Z, Narumoto J. Prevalence of mild behavioral impairment and risk of dementia in a psychiatric outpatient clinic. *J Alzheimer Dis*. 2019;70:505-513. doi:10.3233/JAD-190278
28. Gracia-García P, Modrego P, Lobo A. Apathy and neurocognitive correlates: review from the perspective of "precision psychiatry." *Curr Opin Psychiatry*. 2021;34:193-198. doi:10.1097/YCO.0000000000000677
29. Sherman C, Liu CS, Herrmann N, Lanctôt KL. Prevalence, neurobiology, and treatments for apathy in prodromal dementia. *Int Psychogeriatr*. 2018;30:177-184. doi:10.1017/S1041610217000527
30. Salem H, Suchting R, Gonzales MM, Seshadri S, Teixeira AL. Apathy as a predictor of conversion from mild cognitive impairment to Alzheimer's disease: a Texas Alzheimer's research and care consortium (TARCC) cohort-based analysis. *J Alzheimers Dis*. 2023;92:129-139. doi:10.3233/JAD-220826
31. Fan Z, Wang L, Zhang H, Lv X, Tu L, Zhang M, et al. Apathy as a risky neuropsychiatric syndrome of progression from normal aging to mild cognitive impairment and dementia: a systematic review and meta-analysis. *Front Psychiatry*. 2021;12:792168. doi:10.3389/fpsyt.2021.792168
32. Mortby ME, Adler L, Agüera-Ortiz L, et al. Apathy as a treatment target in Alzheimer's disease: implications for clinical trials. *Am J Geriatr Psychiatry*. 2022;30:119-147. doi:10.1016/j.jagp.2021.06.016
33. Gracia-García P, De-La-Cámara C, Santabárbara J, et al. Depression and incident Alzheimer disease: the impact of disease severity. *Am J Geriatr Psychiatry*. 2015;23:119-129. doi:10.1016/j.jagp.2013.02.011
34. Santabárbara J, Villagrasa B, López-Antón R, et al. Clinically relevant anxiety and risk of Alzheimer's disease in an elderly community sample: 4.5 years of follow-up. *J Affect Disord*. 2019;250:16-20. doi:10.1016/j.jad.2019.02.050
35. Dementia–not all about Alzheimer's. *Lancet* 2015;386:1600. doi:10.1016/S0140-6736(15)00672-8
36. Aarsland D, Ballard C. Psychiatric issues in non-Alzheimer dementias. *Clin Neurosci Res*. 2004;3:397-412. doi:10.1016/j.cnr.2004.04.006
37. Creese B, Ismail Z. Mild behavioral impairment: measurement and clinical correlates of a novel marker of preclinical Alzheimer's disease. *Alzheimers Res Ther*. 2022;14:2. doi:10.1186/s13195-021-00949-7
38. Ismail Z, Leon R, Creese B, Ballard C, Robert P, Smith EE. Optimizing detection of Alzheimer's disease in mild cognitive impairment: a 4-year biomarker study of mild behavioral impairment in ADNI and MEMENTO. *Mol Neurodegener*. 2023;18:50. doi:10.1186/s13024-023-00631-6
39. Andrews SJ, Ismail Z, Anstey KJ, Mortby M. Association of Alzheimer's genetic loci with mild behavioral impairment. *Am J Med Genet B Neuropsychiatr Genet*. 2018;177:727-735. doi:10.1002/ajmg.b.32684

SUPPORTING INFORMATION

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