



Original Article

Phenotyping of mild behavioral impairment domains in multi-regional dementia-free older adults of Chinese ethnicity: impulse dyscontrol as the leading domain

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ABSTRACT

Background: Mild behavioral impairment (MBI) is an early neurobehavioral marker of dementia, yet MBI domain patterns remain underexplored among populations of Chinese ethnicity. This study aimed to characterize MBI domain phenotypes by examining the prevalence of MBI domains and identifying the leading domain across multi-regional cohorts of dementia-free older adults of Chinese ethnicity.

Methods: Data from three previously unpublished datasets (Hangzhou community cohort, China Longitudinal Aging Study and Singapore memory clinic cohort) and three published studies were integrated to estimate the MBI domain prevalence, measured by the Neuropsychiatric Inventory (NPI) and/or MBI-Checklist (MBI-C), through a random-effects meta-analysis. Within the Hangzhou cohort, cross-instrument consistency was evaluated. Exploratory analyses were performed in the Singapore cohort on associations between MBI domains and incident dementia.

Results: Among 1817 participants, impulse dyscontrol was the most prevalent MBI domain, followed by affective dysregulation and decreased motivation, consistently across instruments and cognitive status. In the exploratory longitudinal analyses, impulse dyscontrol was associated with a greater likelihood of incident dementia (HR = 5.05, 95%CI = 2.92 – 8.73).

Conclusions: Impulse dyscontrol was the leading MBI domain among older adults of Chinese ethnicity, with potential clinical relevance for early identification and dementia risk stratification.

1. Introduction

Neuropsychiatric symptoms (NPS) are commonly observed in older adults prior to the onset of dementia [1–3]. Late-life emergent and persistent NPS have been described as mild behavioral impairment (MBI), which is suggested to be a transitional state between normal aging and dementia [4–6]. Critically, MBI has been associated with accelerated cognitive decline and heightened risk of converting to dementia [7–9].

MBI comprises five main domains including decreased motivation, affective dysregulation, impulse dyscontrol, abnormal perception or thought contents and social inappropriateness [4]. Different MBI domains were associated with differential trajectories in converting to all-type dementia [10–12]. For example, individuals with MBI abnormal perception or thought contents (i.e. persistent psychotic symptoms) were associated with a hazard ratio (HR) of 3.8 in dementia conversion (i.e. from normal cognition or mild cognitive impairment to dementia) compared to no NPS individuals [10], while MBI decreased motivation

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(i.e. persistent apathy) exhibited a HR of 2.7 [11]. Previous studies have linked MBI domains such as impulse dyscontrol and affective dysregulation with increased amyloid burden, altered neural patterns and vascular pathology [13–15]. However, findings on MBI domains remain heterogenous across different cohorts, which may hamper the development of effective and specific early-stage interventions for early NPS. Notably, previous studies have shown that study location (i.e. Asian-based vs Non-Asian-based regions) may be one factor underlying the differences in MBI domains prevalence across cohorts [16]. Despite growing recognition of this clinical syndrome, the majority of studies have been conducted in Western regions, and little is known about MBI presentation among older adults of Chinese ethnicity.

Another potential contributing factor to the heterogeneity may be the different measures used to operationalize and detect MBI domains. Based on the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART-AA) MBI criteria, Mild Behavioral Impairment-Checklist (MBI-C) is a recently developed

instrument to detect the presence of MBI and MBI domains in dementia-free individuals [17]. While validation studies of MBI-C have been performed in various cohorts of individuals with subjective cognitive decline and mild cognitive impairment across the world [18–22], the MBI-C remains not as widely used [5,8,9] as the Neuropsychiatric Inventory (NPI) which has been commonly used for assessing NPS in dementia [23]. A published algorithm has been developed to derive MBI domains from NPI items [5,23]. However, the concordance between NPI- and MBI-C- derived domain classification in Chinese dementia-free populations has yet to be thoroughly examined [24].

This study aimed to characterize MBI phenotypes among multi-regional dementia-free older adults of Chinese ethnicity by estimating the prevalence of each domain and identifying the leading domain across cohorts. Using data from unpublished datasets and published studies, we pooled the prevalence of MBI domains across cohorts, with further stratified analyses by instrument and cognitive status. We hypothesized that externalized behaviors such as impulsive and affective

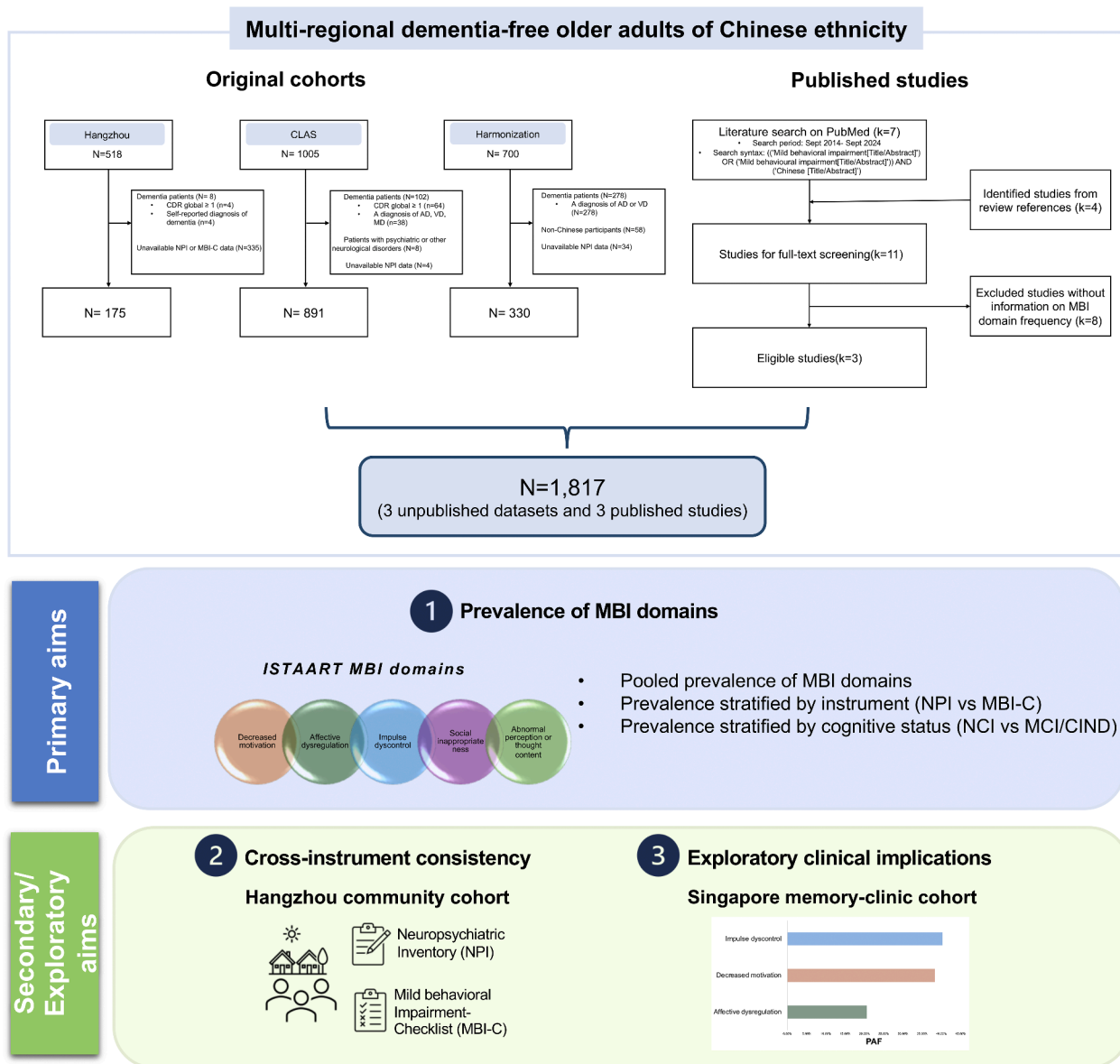


Fig. 1. Study overview.

AD, alzheimer's disease; CDR, clinical dementia rating; CIND, cognitive impairment-no dementia; ISTAART, International Society to Advance Alzheimer's Research and Treatment; MBI, mild behavioral impairment; MBI-C, mild behavioral impairment-checklist; MCI, mild cognitive impairment; MD, mixed dementia; MoCA, montreal cognitive assessment; NCI, no cognitive impairment; NPI, neuropsychiatric inventory; PAF, population-attributable fractions; VD, vascular dementia.

symptoms would be more prevalently reported in these cohorts. In light of recent discussions on the feasibility of operationalizing MBI using the NPI [25], we also performed sensitivity analyses in a longitudinal cohort applying more stringent criteria to evaluate whether the same pattern of domains would emerge. To further support the robustness of these prevalence estimates, we additionally examined the cross-instrument consistency between NPI and MBI-C. Finally, we conducted exploratory analyses to evaluate the association between individual domains and incident dementia and to estimate the population-attributable fractions (PAFs) as indicators of their population-level prognostic contribution.

2. Methods

2.1. Study cohorts

Data were obtained from two community-based cohorts in China and a memory-clinic based cohort in Singapore (Fig. 1; Table 1). In the Hangzhou cohort, participants were recruited from 11 communities in Gongshu District, Hangzhou, China from June 2022 [26]. The China Longitudinal Aging Study (CLAS) is a community-based longitudinal cohort examining Chinese older adults at baseline, as well as at 1st and 3rd year for follow-up assessment [27,28]. The Singapore memory clinic cohort is a multi-ethnic longitudinal cohort which examined mainly memory clinic-based participants at baseline and during follow-up annually up to a maximum of 5 years [29,30]. The Singapore study was included because the main ethnicity in Singapore is Chinese (74%) [31], which provides valuable representation of Chinese adults beyond mainland China and hence enhances the generalizability across regions of predominantly Chinese ethnicity. In the current study, we primarily analyzed cross-sectional data at baseline to examine the optimal use of NPI in the studies of MBI syndrome and the prevalence of MBI domains, with additional sensitivity and exploratory analyses in the Singapore memory-clinic cohort with longitudinal data to confirm the robustness of our findings.

To meet the ISTAART-AA criteria of MBI, in all datasets, we included participants who were 1) age ≥ 50 years old; 2) administered NPS

measures; 3) of Chinese ethnicity. Exclusion criteria included: 1) patients diagnosed with major depression or other major mental illnesses; 2) patients with malignant diseases, such as cancers; patients with symptoms of substance abuse; 3) patients with severe visual, auditory or communication disorders; 4) patients with a diagnosis of dementia. Dementia status was determined using cohort-specific approaches: a global Clinical Dementia Rating (CDR) score ≥ 1 or self-reported medical history of diagnosed dementia in the Hangzhou cohort [32,33]; a global CDR score ≥ 1 or clinician diagnosis of dementia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) in the CLAS cohort [27,28]; and multidisciplinary consensus incorporating comprehensive neuropsychological, laboratory and neuroimaging assessments based on DSM-IV criteria in the Singapore memory clinic cohort [29,30].

Written informed consent was obtained from all participants or their legally acceptable representative across all cohorts. All studies were approved by the respective institutional review board.

2.2. Neuropsychiatric symptom (NPS) measures

The Mild Behavioral Impairment-Checklist (MBI-C) is an assessment tool designed specifically for capturing MBI symptoms, in accordance with the ISTAART-AA MBI criteria [17]. The MBI-C has been validated in multiple languages and the simplified Chinese-validated version was used in the current study [20]. The MBI-C comprises of 34 items, assessing five domains: 1) decreased drive/motivation (6 items, 0–18 points); 2) affective dysregulation (6 items, 0–18 points); 3) impulse dyscontrol (12 items, 0–36 points); 4) social inappropriateness (5 items, 0–15 points); and 5) abnormal perception and thought content (5 items, 0–15 points). Informants were asked to provide either 'Yes' or 'No' for each question, with a 'Yes' indicating a change in the participants' behaviors or personality that started after the participant turned 50 years old and has persisted for at least 6 months. The presence of each question was recorded (response 'Yes' or 'No'), followed by the severity (1 = mild, 2 = moderate, 3 = severe) for each symptom. Domain scores of MBI-C were calculated by summing the severity of relevant items, with domain presence defined as a score ≥ 1 .

Table 1
Participant characteristics of unpublished datasets and published studies.

Author	Year	Region	Study	N	Mean age	Age range	Sex (F,n, %)	MoCA ^a	Cognitive status ^b	Measures of MBI domains	Operationalized definitions
Unpublished datasets		Hangzhou	Community-based cohort	175	72.4 (9.7)	51–94	110 (62.9%)	7.66 (2.88) ^c	NCI: 89 (50.9%) MCI/CIND: 71 (40.6%)	MBI-C/NPI (Informant-rated)	MBI domain ≥ 1 ; MBI domains based on the established NPI algorithm at baseline
		Shanghai	CLAS	891	71.9 (8.2)	50–96	510 (57.2%)	21.96 (6.13)	NCI: 409 (45.9%) MCI/CIND: 482 (54.1%)	NPI (Informant-rated)	MBI domains based on the established NPI algorithm at baseline
		Singapore	Harmonization Memory clinic cohort	330	71.8 (7.7)	50–95	178 (53.9%)	21.61 (5.08)	NCI: 112 (33.9%) MCI/CIND: 218 (66.1%)	NPI (Informant-rated)	MBI domains based on the established NPI algorithm at baseline
Chen et al.	2022	Taiwan	Community-based cohort	202	65.6 (6.9)	≥ 50	113 (55.9%)	26.67 (2.33)	-	MBI-C (Informant-rated)	MBI domain ≥ 1
Cui et al.	2024	Beijing	HC from community cohort	82	62.9 (9.1)	≥ 50	57 (69.5%)	26 (3) ^d	-	MBI-C (Informant-rated)	MBI domain ≥ 1
Fan et al. ^e	2020	Guangdong	Primary care clinic cohort	137	69.6 (7.6)	60–90	94 (68.6%)	25.8 (2.5)	-	MBI-C (Respondent source unclear)	MBI domain ≥ 1 ^e

^a Full MoCA ranged 0–30 was conducted in these cohorts.

^b Cognitive status was determined in the unpublished datasets using cohort-specific approaches. Comparable information on cognitive status/stage was not available in the published studies.

^c A 5 minute MoCA ranged 0–12 was conducted in the Hangzhou community cohort. n = 15 have no available MoCA data.

^d Median and interquartile values were reported.

^e Prevalence estimates were extracted from Pan et al [16].

The Neuropsychiatric Inventory (NPI) is an informant-based questionnaire assessing NPS of participants with a one-month reference range. The NPI is a reliable and validated assessment for NPS in various neuropsychiatric disorders including dementia [23,24]. The validated NPI-Chinese version (CNPI) [34] was used in the current study. The NPI assesses NPS on 12 domains including 10 behavioral symptoms (i.e. delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, disinhibition, apathy/indifference, irritability/lability, aberrant motor behaviors) and 2 neurovegetative symptoms (i.e. nighttime behavior and appetite). The presence (response as 'Yes' or 'No'), the severity (1=mild, 2=moderate, 3= marked), the frequency (1=occasionally, 2=often, 3= frequently, 4=very frequently) of the NPS domain were evaluated. The sum of severity x frequency of each item was calculated. MBI domains measured by NPI were calculated following an established algorithm based on the ISTAART-AA criteria including 1) decreased drive/motivation (NPI apathy); 2) affective dysregulation (NPI depression, anxiety and elation); 3) impulse dyscontrol (NPI agitation, irritability and aberrant motor behaviors); 4) social inappropriateness (NPI disinhibition); and 5) abnormal perception and thought contents (NPI hallucination and delusion) [5,35]. As the NPI captures symptoms with a one-month reference window, NPI-derived MBI domain classification was considered in the current study as a proxy measure rather than a full equivalent of MBI-C or syndromic MBI. The presence of an MBI domain was defined as a domain score ≥ 1 .

2.3. Cognitive assessments

In the Singapore memory clinic cohort, the cognitive status of participants, including no cognitive impairment (NCI), cognitive impairment-no dementia (CIND) and dementia at baseline and during follow-up was determined based on the standardized neuropsychological assessments and the DSM-IV criteria [29]. In the CLAS, cognitive status was determined using the CDR Global Scores, where NCI = 0, mild cognitive impairment (MCI) = 0.5 and dementia ≥ 1 [33,36]. The Montreal Cognitive Assessment (MoCA; range 0–30) was also employed to assess the global cognitive functioning in both the CLAS and memory-clinic based studies [27,29]. In the Hangzhou cohort, global cognitive functioning was evaluated using the established cognitive assessment including the CDR and the 5min-MoCA. The 5 min MoCA (range 0–12) was designed to assess memory, verbal fluency and orientation, which has been validated and applied for screening in large-scale community studies [37,38]. The 5 min MoCA cutoff of ≤ 7 was used to identify cognitive impairment for the stratified analyses [33, 37].

2.4. Statistical analyses

2.4.1. Prevalence estimates of MBI domains

The prevalence of five MBI domains measured by NPI or MBI-C was calculated for the three previously unpublished study cohorts. Furthermore, we performed a literature review in September 2024 and included published studies in the last 10 years with available MBI domain information on prevalence in cohorts of Chinese dementia-free participants, including eligible studies identified in reviews (Fig. 1). Published papers available in full-text and written in English with available information on the frequency of MBI domains were included (Detailed screening methods in Supplementary Table 1).

Participant characteristics of the three unpublished datasets were summarized using the mean (standard deviation, SD) for continuous variables and number (percentage) for categorical variables. The measurement instruments and operationalized definition for MBI domains were also reported. Study characteristics of published studies including sample size, demographics, cognitive status, assessment instrument and operationalized definitions, as well as the prevalence of MBI domains were extracted.

We further employed random-effects meta-analysis to generate the pooled prevalence of MBI domains across the available cohorts of unpublished datasets and published studies (Supplementary Methods). The heterogeneity of the studies was calculated using the Cochrane Q and I^2 statistics. Publication bias was also assessed using funnel plots (Supplementary Figure 1). Of note, in the primary analyses of pooled prevalence, only one estimate was included per cohort to avoid duplication (i.e. estimates derived from MBI-C will be used if both MBI-C and NPI estimates were available). Following the same procedure, we further conducted stratified meta-analyses to compare the pooled prevalence of MBI domains derived from the MBI-C and NPI measures, as well as to compare the pooled prevalence of MBI domains in the NCI and MCI/CIND groups. Three sets of sensitivity analyses were further performed to examine the robustness of the findings, including analyses restricted to informant-rated studies, comparison of MBI-C prevalence between original and published cohorts and application of a more stringent two consecutive visits (TCV) criterion in the Singapore memory clinic cohort (Supplementary Methods).

2.4.2. Instrument consistency of MBI domains between NPI and MBI-C

In the Hangzhou cohort, we quantified the agreement between NPI- and MBI-C-derived classification for each MBI domain using the Cohen's κ . The agreement between two measures in classification is slight (κ : 0.00 - 0.20), fair (κ : 0.21 - 0.40), moderate (κ : 0.41 - 0.60), substantial (κ : 0.61 - 0.80) and almost perfect (κ : 0.81 - 1.00) [39]. Further exploratory analyses of NPI-to-MBI-C item mapping, as well as NPI symptom co-occurrence patterns within the impulse dyscontrol domain were performed to evaluate the instrument consistency (Supplementary Methods).

2.4.3. Exploratory analyses on associations between MBI domains and longitudinal cognitive outcomes

In the Singapore memory clinic cohort, further exploratory analyses were performed to explore the longitudinal associations between MBI domains and cognitive outcomes, controlling for age, sex and cognitive status (NCI vs CIND) at baseline. Cox regression models were fitted to examine the associations between MBI domains, defined using the stringent TCV criterion, and incident dementia, with proportional hazards assumptions evaluated (Supplementary Methods). Participants who developed a MBI domain at any follow-up visit were assigned a participant-specific baseline at the first onset visit [25], which was used to maximize the study sample by retaining individuals who developed domains during follow-up. Time-to-dementia was measured from that visit to dementia diagnosis (in years) to reflect the emergence of clinically relevant symptoms rather than study entry. For participants without the domain, baseline was defined as the first study visit. Covariates of age, sex and cognitive status was recorded for the participant-specific baseline accordingly. Based on the prevalence (p) and adjusted hazard ratios (HRs), population-attributable fractions (PAFs) were computed using Levin's formula $PAF = \frac{p(HR-1)}{1+p(HR-1)}$. These estimates were used to reflect the potential population-level prognostic contribution of each MBI domain and were not interpreted as measures of causal preventability.

Descriptive analyses were conducted using SPSS (IBM SPSS Statistics, version 29.0.2.0(20)), and all other statistical analyses were performed in R 4.4.2 using RStudio (version 2024.12.0.467).

3. Results

3.1. Prevalence of MBI domains in cohorts of dementia-free older adults of Chinese ethnicity

3.1.1. Overview of included studies and participant characteristics

A total of 1817 participants from three unpublished cohorts of participants of Chinese ethnicity and from three published studies [40–42]

were studied (Fig. 1; Table 1). The current study only included prevalence of MBI domain data in the dementia-free participants, who were recruited from the community, memory or primary-care clinics.

3.1.2. Prevalence of MBI domains

Among all eligible studies, the impulse dyscontrol domain consistently emerged as the most prominent MBI domain, followed by affective dysregulation and decreased motivation (Fig. 2). In the random-effects meta-analyses, the pooled prevalence estimates were 27% (95%CI = 8 – 52%) for impulse dyscontrol, 22% (95%CI = 6 – 43%) for affective dysregulation and 18% (95%CI = 4 – 39%) for decreased motivation. Social inappropriateness and abnormal perception or thought content were less frequent across studies, with pooled prevalence estimates of 8% (95%CI= 1 – 18%) and 6% (95%CI = 2 – 10%).

Subgroup analyses were performed to compare the prevalence estimates of MBI domain measured by NPI and MBI-C, respectively (Fig. 3). Findings from MBI-C informant measures showed a similar pattern that

the most common domain was impulse dyscontrol, followed by affective dysregulation and decreased motivation. A similar ranking was observed using the NPI, although the prevalence estimates were generally lower.

When examining the MBI domain prevalence across cognitive status in the three unpublished datasets, a consistent trend was observed across the NCI and MCI/CIND groups, with the impulse dyscontrol remaining the most prevalent domain and social inappropriateness the least frequent domain (Fig. 4).

3.1.3. Sensitivity analyses of MBI domain prevalence

We conducted sensitivity analyses in studies that employed informant-rated measures for MBI domains. These analyses demonstrated consistent domain ranking patterns as the main analyses, with lower pooled estimates and narrower confidence intervals, supporting the robustness of the primary findings (Supplementary Figure 2 and Supplementary Figure 3). We further compared the MBI-C prevalence in

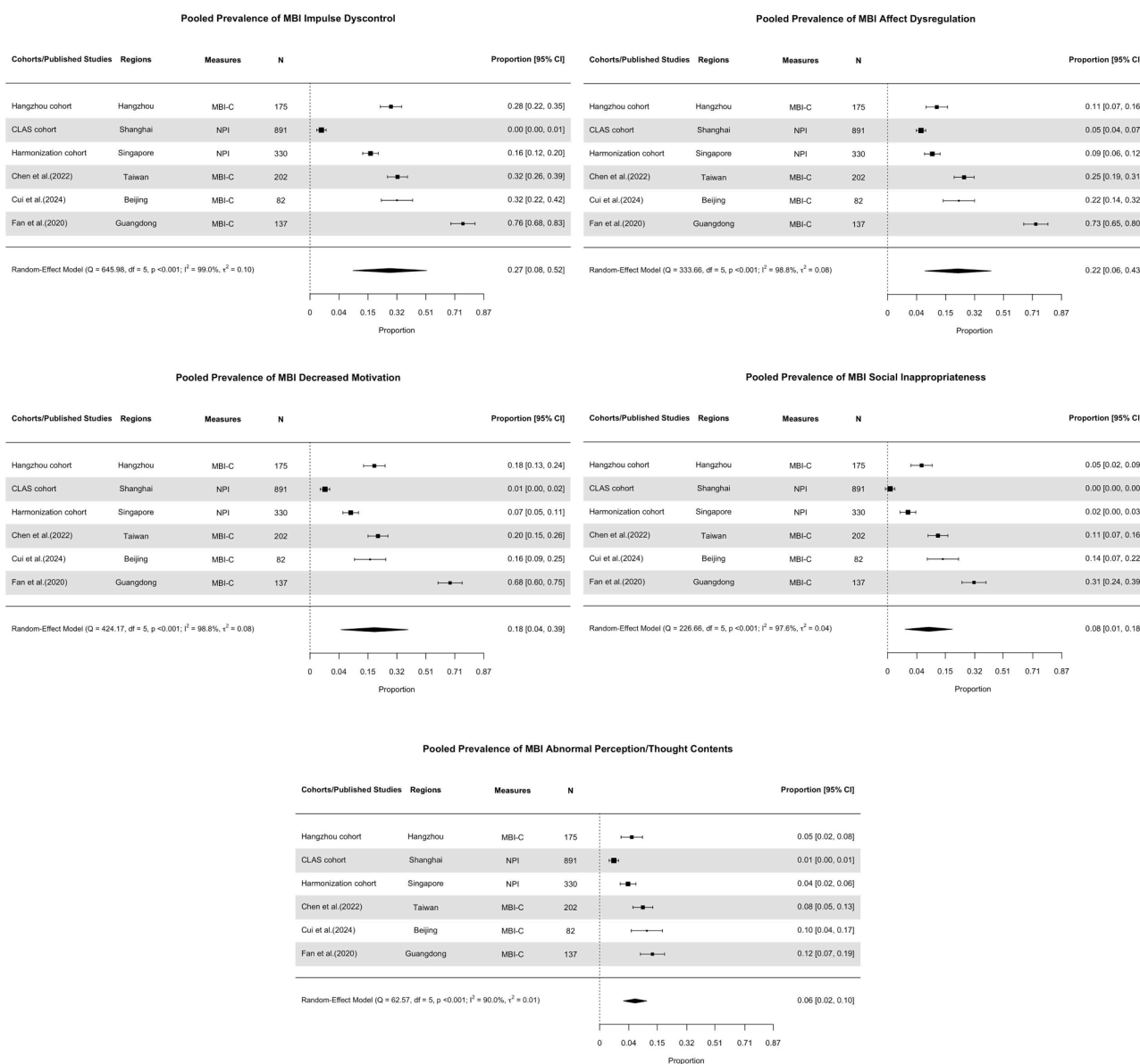


Fig. 2. Pooled prevalence of MBI domains in cohorts of dementia-free participants of Chinese ethnicity.

For the Hangzhou cohort, which provided both NPI and MBI-C estimates of MBI domains, the MBI-C estimate was selected for the primary analyses as it aligns most closely with the operationalized definition of MBI. For the [41], the informant-rated estimate was selected for primary analyses. For the [40], the prevalence estimate of MBI domains was extracted from the published review of [16].

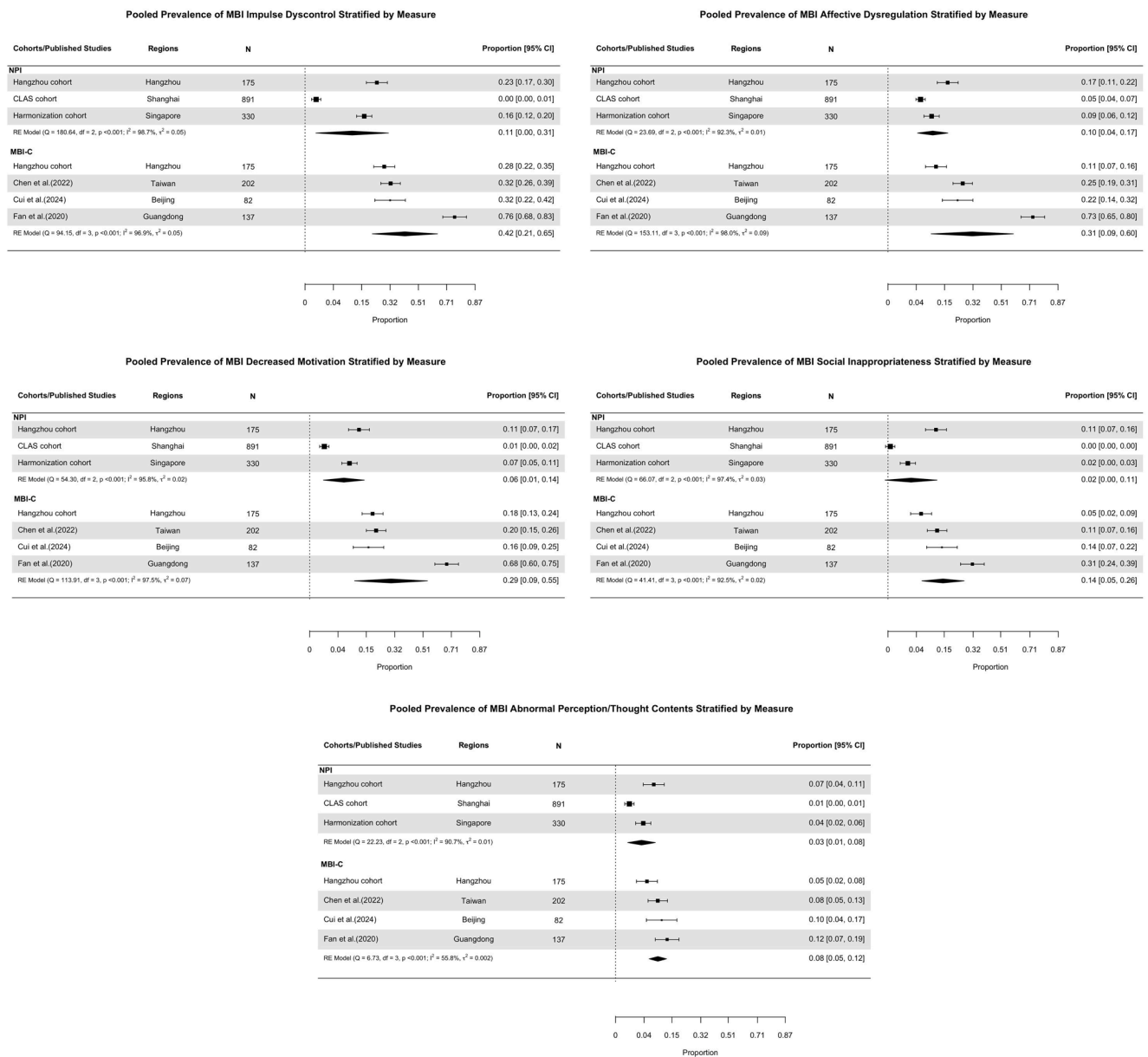


Fig. 3. Comparison in the prevalence of MBI domains in dementia-free participants of Chinese ethnicity between measures of NPI and MBI-C.

the Hangzhou cohort with the pooled prevalence data from the published studies, which showed a generally lower prevalence of MBI domains in the Hangzhou cohort (Supplementary Figure 4). However, when the comparison was restricted to community-based cohorts only (i.e. Chen et al., 2022 and Cui et al., 2024) [41,42], we showed comparable results in the following domains: impulse dyscontrol, decreased motivation and abnormal perception or thought content (Fig. 3; Supplementary Figure 4).

Given the cross-sectional nature of included studies, we also performed sensitivity analyses to examine the prevalence of MBI domains using longitudinal NPI assessments over a study period of 6 years (Singapore memory clinic cohort). Based on the criteria of the presence of symptoms for TCV, impulse dyscontrol (17%) remained as the leading domain, followed by decreased motivation (9%) and affective dysregulation (8%) (Supplementary Table 2).

3.2. Instrument consistency in MBI domains between NPI and MBI-C

As the Hangzhou cohort included both NPI and MBI-C assessments,

participants are summarized to further contextualize the cross-instrument consistency analyses. The Hangzhou cohort comprises of a total of 175 participants with available NPI and informant-based MBI-C responses (Table 1), with 38.3% (n = 67) of the participants exhibited any MBI domains (MBI-C scores ≥ 1). To examine the utility of NPI in detecting MBI domains, we evaluated the concordance between NPI and MBI-C derived domains. For agreement of MBI domains identified between NPI and MBI-C measures, the Cohen's Kappa showed substantial agreement for impulse dyscontrol ($\kappa = 0.64$), affective dysregulation ($\kappa = 0.62$) and abnormal perception or thought content ($\kappa = 0.78$), moderate agreement for decreased motivation ($\kappa = 0.55$) and fair agreement for social inappropriateness ($\kappa = 0.39$) (Supplementary Figure 5A). These findings were further supported by the NPI-to-MBI-C item-domain mapping across all MBI domains (Supplementary Figure 5B), as well as the exploratory factor analysis on NPI co-occurring symptoms in individuals with impulse dyscontrol (Supplementary Table 3).

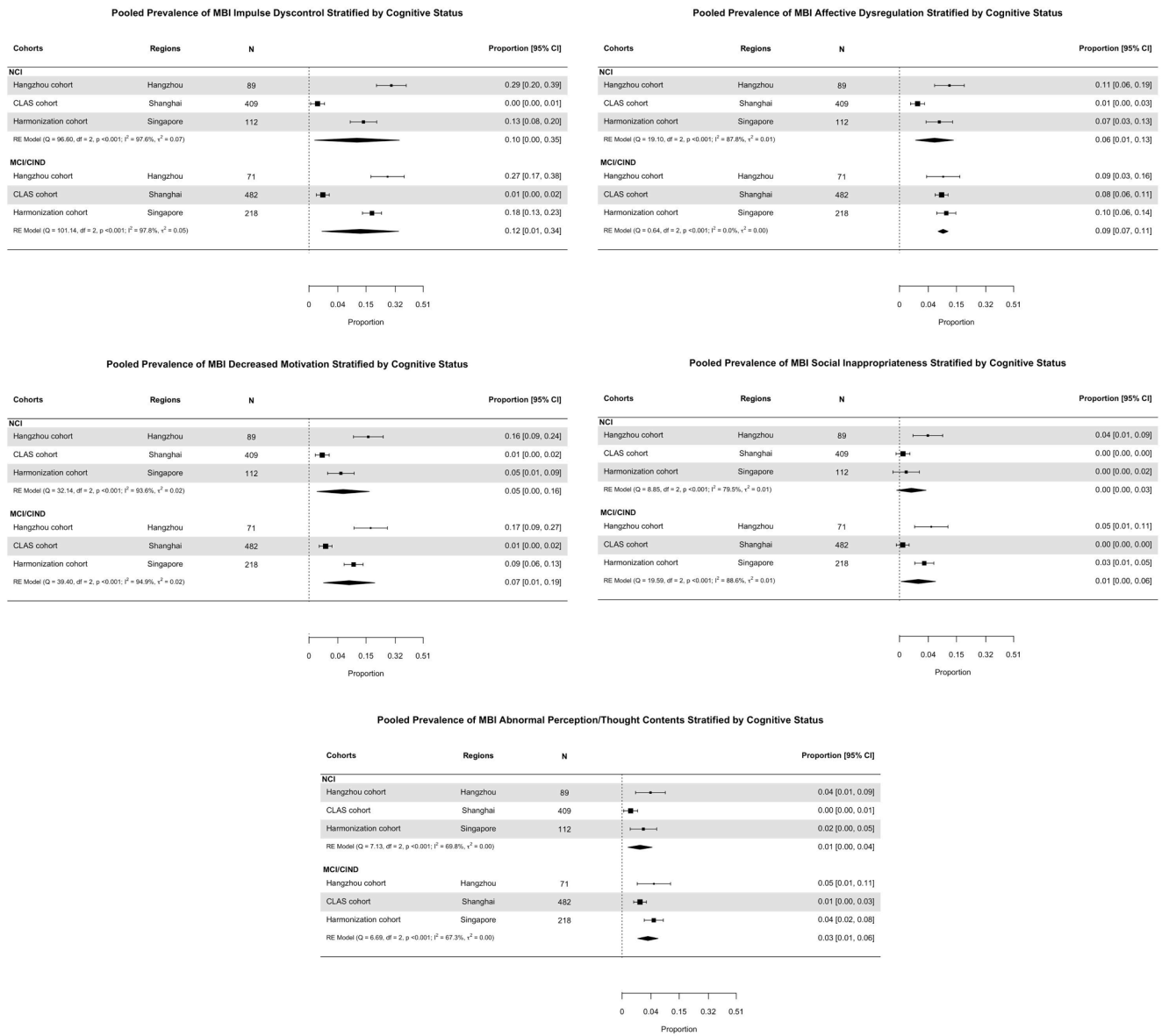


Fig. 4. Prevalence of MBI domains in dementia-free participants of Chinese ethnicity stratified by cognitive status. Stratified analyses by cognitive status were performed on the three unpublished datasets. For the Hangzhou cohort, the MBI-C estimate was used in the current analyses.

3.3. Exploratory analyses on longitudinal associations between MBI domains and cognitive outcomes

The Singapore memory clinic cohort had 302 subjects with available longitudinal data during the follow-up period of up to five years. We computed the HRs and PAFs for MBI domains in association with incident dementia as exploratory analyses (Supplementary Table 2). While the following domains were associated with incident dementia, presence of impulse dyscontrol was found to have the largest PAF (40.3%), followed by decreased motivation (38.3%) and affective dysregulation (20.6%). Social inappropriateness and abnormal perception or thought content were rare in the current sample (1% and 2% respectively), resulting in sample sizes too small to support reliable statistical analyses.

4. Discussion

This study is the first to examine the phenotypic patterns of MBI domains in older adults of Chinese ethnicity across multiple regions. In

three unpublished datasets and three published studies, we identified MBI domains based on the operationalized definitions in the ISTAART-AA criteria, showing that impulse dyscontrol is the leading MBI domain among multi-regional cohorts. To support the robustness of prevalence patterns, we further showed that MBI domain identification demonstrated moderate to high agreement between the NPI and MBI-C for most domains and the findings of MBI domain prevalence were consistent across these two primary measures for MBI. For exploratory analyses, impulse dyscontrol showed the highest PAF for incident dementia, suggesting potential prognostic relevance in pre-dementia populations.

While MBI has been increasingly recognized as a critical marker for early identification and intervention, many studies have focused on examining MBI as a unitary construct. However, it is imperative to note the heterogeneous presentation of different MBI domains, especially across different cultures. Utilizing a meta-analytic approach, our study showed that impulse dyscontrol was the most frequently observed domain, followed by affective dysregulation and decreased motivation,

consistent cross cognitive groups (i.e. NCI vs MCI/CIND). Symptoms of impulse dyscontrol including agitation and impulsivity are associated with a high risk of incident cognitive decline and dementia conversion [43,44]. Although our exploratory longitudinal analyses were based on a relatively small sample, we similarly found that impulse dyscontrol predicted incident dementia and displayed the highest PAF in the exploratory analyses. Previous studies have linked impulse dyscontrol with increased tau and amyloid burden [45,46], as well as structural and functional alterations in the fronto-parietal region implicated in NPS in AD [13,47]. Notably, higher microvascular burden in these brain regions was associated with impulse dyscontrol-related symptoms in MCI and AD [48]. Furthermore, decreased plasma insulin levels were observed in impulse dyscontrol, which was consistent with previous findings of increased agitation and irritability in diabetes among AD patients [49,50]. Together, these studies suggest that vascular and metabolic dysfunction may represent plausible mechanisms underlying impulse dyscontrol. Given the high prevalence of cerebrovascular and metabolic diseases observed in the Chinese populations [51,52], these mechanisms may warrant further investigation in dementia free individuals of Chinese ethnicity.

A recent systematic review on MBI domains, which predominantly included western cohorts and showed that affective dysregulation (32%) was the most prevalent MBI domain [16]. While both affective dysregulation and impulse dyscontrol were often the leading domains in individual studies across different regions [16,53], symptoms such as agitation and impulsive behaviors could be more externalized and visible to the caregivers in the Chinese cultures, while some affective symptoms such as emotional distress or withdrawal could be under-recognized or normalized by the Chinese caregivers. This is in concordance with findings of Chinese caregivers showed less sensitivity towards depression and apathy symptoms of AD patients [54]. This pattern may partly reflect cultural differences on symptom recognition, particularly for externalized behaviors, although further validation in more comparable cohorts is needed. Additionally, symptoms of irritation and aberrant motor behaviors were respectively linked to 14.7 and 17.5 additional hours of active care and supervision per week, which may cause more distress and noticeability [55]. Previous studies have highlighted the effect of study partner characteristics on reporting NPS across all cognitive stages [56]. Although caregivers' information was not ascertained in the current study, future studies should aim to understand the associations between MBI domains and caregiver characteristics (e.g. sex, age and education), which could help aid early identification and intervention for early behavioral symptoms.

To address the commonly noted limitation of NPI's one-month assessment window in MBI studies, we examined agreement between NPI and MBI-C in the Hangzhou cohort and compared the prevalence estimates across instrument. We found that impulse dyscontrol domain remained the leading MBI domain across instruments. Furthermore, we performed sensitivity analyses by employing a more stringent criterion for MBI case identification (i.e. TCV) [25], showing that impulse dyscontrol remained as the most prevalent domain over a maximum of six-year study period. However, while most of the domains showed high agreement, NPI and MBI-C only demonstrated fair agreement in the domain of social inappropriateness. This is particularly consistent with the previous literature that social inappropriateness was less endorsed in the Chinese cohorts [20,57]. In the current transformation algorithm framework, social inappropriateness only consists of the *NPI disinhibition* item. For NPI administration, the screening questions of NPI disinhibition included 'Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?' [23], which may not fully capture impaired social cognition among Chinese dementia-free population. Experimental studies are needed to understand the presentation and mechanisms of impaired social cognition (i.e. theory of mind, perception of social cues), as it has been linked to greater dementia risk, including both AD and behavioral variant frontotemporal

dementia [58]. Additionally, under the cultural belief of maintaining harmony and social reputation [54,59], we hypothesized that stigma of certain MBI domains (e.g. social inappropriateness) could also be a contributing factor for NPS identification, which may contribute to the differences in prevalence estimates of these domains across studies. Thus, future studies should develop measures with questions that are more sensitive to capture these symptoms under a different cultural context.

From the supplementary item-mapping analyses, we showed that the leading endorsed NPI items within each MBI-C domain were in concordance with the established transformed algorithm (Supplementary Figure 5) [5]. Of note, while NPI-nighttime disturbances are not included in the current definition of MBI, it is frequently observed in those with MBI-C domains such as impulse dyscontrol and affective dysregulation. Thus, it is important to take into consideration of the comorbid symptoms of sleep disturbances in research as well as clinical practice as the critical symptom presentation of early behavioral disturbances. Beyond instrument concordance, exploratory factor analysis within the MBI-C impulse dyscontrol group suggested two preliminary patterns of NPI symptom co-occurrence, including one capturing externalizing symptoms (agitation, irritability, disinhibition, hallucination and delusion) and another capturing affective symptoms (depression, anxiety and apathy). However, given the limited sample size of participants who endorsed other MBI-C domains, these findings should be considered preliminary and hypothesis-generating, and larger studies are needed to further validate patterns of NPS co-occurrence across different MBI domains.

While our study provided generalizable findings for multi-regional Chinese older adults, several limitations should be considered. First, high heterogeneity was observed across the included studies, which may reflect differences in the recruitment facilities (i.e. the community, primary care clinic and specialist memory clinic), the reporting sources and the approaches used to ascertain cognitive status across cohorts. Although sensitivity analyses restricted to informant-rated studies and supportive stratified analyses by cognitive status both showed consistent overall patterns and narrower confidence intervals, these between-study differences should be considered when interpreting the pooled estimates from the primary analyses. Future studies are encouraged to have harmonized recruitment strategies, standardized behavioral and cognitive measures and biomarker-informed subgrouping, which may further clarify and validate the prevalence patterns of MBI domains. Second, while individuals with a history of primary psychiatric illness were excluded and standardized measures such as the NPI and MBI-C were used to capture late-life emergent behavioral changes, retrospective ascertainment of these domains in existing cohorts remains inherently difficult. Therefore, the potential influence of pre-existing behavioral or emotional traits unrelated to neurodegenerative disease cannot be fully excluded. Third, while we performed exploratory longitudinal analyses to further examine the persistence of MBI domains measured using the NPI, we acknowledge that this approach may introduce time-related bias and should be considered when interpreting these exploratory findings. In addition, PAFs may overestimate the proportion of dementia cases that are theoretically preventable. MBI represents a prodromal stage of neurodegenerative disease, and its emergence likely reflects the same underlying pathology that may lead to dementia. As such, removing MBI symptoms alone would not alter the disease process. Therefore, PAFs in this study are better understood as indicators of the population-level prognostic contribution of each MBI domain to cognitive decline, rather than as estimates of causal preventability.

5. Conclusion

To conclude, impulse dyscontrol is the leading MBI domains among dementia-free older adults of Chinese ethnicity. This domain was additionally associated with poorer cognitive outcomes and greater PAF for incident dementia. Importantly, we showed that NPI and MBI-C showed

adequate agreement between each other and the established NPI-to-MBI mapping algorithm could serve as a proxy measure for capturing MBI domains among Chinese participants. Future studies are encouraged to further examine the overlapping NPS symptom profile across MBI domains, as well as investigate the caregiver profiles for early behavioral symptoms, which would aid the development of more tailored early identification and intervention for at-risk individuals.

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Consent statement

Written informed consent was obtained from study participants before study enrollment.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

During the preparation of this work the authors used ChatGPT to assist with grammar checking in the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Data statement

All data supporting the findings of this study are available upon request.

CRediT authorship contribution statement

Yingqi Liao: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Yaping Zhang:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Haoran Zhang:** Writing – review & editing, Methodology, Data curation. **Yan Li:** Writing – review & editing, Methodology. **Dylan X. Guan:** Writing – review & editing, Methodology. **Yifan Yan:** Writing – review & editing, Data curation. **Yue Ling Chai:** Writing – review & editing. **Mitchell K.P. Lai:** Writing – review & editing. **Shifu Xiao:** Writing – review & editing, Funding acquisition. **Christopher L. H. Chen:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Xin Xu:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The 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.

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Supplementary materials

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