Gender/sex differences in the association of mild behavioral impairment with cognitive aging

Katrin Wolfova[a,b,c], Byron Creese[d], Dag Aarsland[e,f], Zahinoor Ismail[g,h], Anne Corbett[i], Clive Ballard[h], Adam Hampshire[j], Pavla Cermakova[b,c]

[a] *Department of Psychiatry and Medical Psychology, Third Faculty of Medicine, Charles University, Ruska 87, 100 00 Prague, Czech Republic*
[b] *National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic*
[c] *Department of Epidemiology, Second Faculty of Medicine, Charles University, Plzenska 130/221, 150 00 Prague, Czech Republic*
[d] *University of Exeter Medical School, College of Medicine and Health, RILD Building, RD&E Hospital Wonford, Barrack Road, Exeter, EX2 5DW, UK*
[e] *Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF, UK*
[f] *Centre for Age-Related Medicine, Stavanger University Hospital, 4000 Stavanger, Norway*
[g] *Departments of Psychiatry and Clinical Neurosciences; Hotchkiss Brain Institute; University of Calgary, Canada*
[h] *University of Exeter Medical School, College of Medicine and Health, St Luke's Campus, University of Exeter, Exeter EX1 2LU, UK*
[i] *South Cloisters, College of Medicine & Health, St Luke's Campus, University of Exeter, Exeter EX1 2LU, UK*
[j] *Faculty of Medicine, Department of Medicine, Imperial College London, London SW7 2AZ, UK*

Running title: Gender/sex differences in mild behavioral impairment

Correspondence:
Pavla Cermakova, MD, PhD
Second Faculty of Medicine
Charles University
V Úvalu 84, 150 06 Prague 5
Czech Republic
Pavla.Cermakova@lfmotol.cuni.cz
+420 257 296 482

ABSTRACT

BACKGROUND: While the gender/sex differences in neuropsychiatric symptoms in dementia population are well described, gender/sex differences in mild behavioral impairment (MBI) in dementia-free populations and the relationship to cognitive performance and to subsequent cognitive decline have not been studied.

OBJECTIVE: We aimed to explore gender/sex differences in the association of MBI with the level of cognitive performance and its rate of decline in a dementia-free cohort.

METHODS: We studied 8,181 older adults enrolled in the online PROTECT UK Study. MBI was assessed using the MBI Checklist and cognition was measured by digit span, paired associate learning, spatial working memory and verbal reasoning. Statistical analysis was conducted using linear regression models and linear mixed-effects models.

RESULTS: Out of 8 181 individuals (median age 63 years, 73% females), 11% of females and 14% of males had MBI syndrome. Females exhibited less often symptoms of decreased motivation (45% vs. 36% in males), impulse dyscontrol (40% vs. 44% in males; $p=0.001$) and social inappropriateness (12% vs. 15%; $p<0.001$), while they showed more often symptoms of emotional dysregulation (45% vs. 36%; $p<0.001$). The associations of MBI domains with some measures of cognitive performance and decline were stronger in males than females, with the exception of the association of emotional dysregulation with the rate of cognitive decline in verbal reasoning, which was present exclusively in females.

CONCLUSION: MBI may influence cognition to a greater extent in males than in females. We propose that predictors and biomarkers of dementia should consider gender/sex as an effect modifier.

Keywords: cognition, sex differences, gender differences, behavioral symptoms, dementia

BACKGROUND

Females bear a higher burden of dementias than men in terms of prevalence, incidence, and also severity [1]. Two thirds of patients with Alzheimer disease (AD) , the most common cause of dementia [2], are females [3]. While multiple cognitive abilities are affected by AD more adversely in females [4], males experience steeper cognitive decline when affected by other forms of dementia [5]. Gender/sex differences in cognitive functioning exist also in healthy older adults, with males performing better in some visuospatial tasks, whereas females outperform males in tasks focused on verbal domains [6]. Many new biomarker studies are rapidly emerging but only few consider gender/sex as a moderator [7]. It is crucial to understand the contribution of gender/sex in the variations in cognitive aging to optimize prevention and intervention strategies.

There is a need to develop more sensitive measures to accurately identify individuals at a higher risk of incident cognitive decline. Mild behavioral impairment (MBI) is a promising indicator of a population at risk. MBI is characterized by a persistent change in personality or behavior starting later in life, represented by the emergence of neuropsychiatric symptoms (NPS) such as apathy, anxiety, mood disturbances, agitation, disinhibition, lack of empathy, loss of insight, or psychosis [8]. MBI is associated with faster cognitive and functional decline.[9, 10] Also individual NPS, especially anxiety and irritability, have been found to be related to cognitive decline [11, 12]. Moreover, several studies report links between MBI and neurobiological markers, such as higher β-amyloid deposition, lower plasma Aβ42/Aβ40, tau pathology, and neurodegeneration in pre-dementia population [13-16]. While gender/sex differences in non-cognitive manifestations are well described in dementia population [17-19], little is known about these differences in individuals without dementia.

Previous studies suggest that the prevalence of MBI – specifically decreased motivation, impulse dyscontrol, apathy, agitation, and irritability – in a cognitively healthy population might be higher in males [20-22]. It is plausible to hypothesize that gender/sex might play a role not only in the prevalence of individual NPS but might also moderate the relationship between NPS and cognition in dementia-free populations. In the present study, we aimed to explore gender/sex differences in MBI and its associations with the level of cognitive performance and the rate of cognitive decline in a large sample of community-dwelling dementia-free individuals from the United Kingdom.

METHODS

Source of data

We utilized data from the Platform for Research Online to Investigate Genetics and Cognition in Aging (PROTECT, https://www.protectstudy.org.uk/), a longitudinal online research project that collects data from ~25,000 healthy individuals in the United Kingdom. The first wave of data collection started in November 2015 and has been followed by subsequent assessments on a yearly basis. In addition, refreshment samples are added annually to keep the sample size steady. Eligible participants and informants 1) are based in the United Kingdom, 2) have a good understanding of English, 3) are 50 years old or over, 4) have regular access to a computer and the internet, and 5) were not diagnosed with dementia. The absence of a diagnosis of dementia was self-reported by participants. If participant's cognitive performance measured during follow-up is significantly lower than age-matched norms at two consecutive time points, then data is reviewed by a study clinician. If they agree there is cause for concern, the participant is contacted and is recommended referral to their GP for further assessment.

Participants are then obliged to withdraw if they received a dementia diagnosis. All participants provided informed consent via online platform and all data were pseudo-anonymized. The study was approved by London Bridge National Research Ethics Committee (Reference: 13/LO/1578).

Mild behavioral impairment

MBI was assessed using the Mild Behavioral Impairment Checklist (MBI-C) rated by informants. MBI-C comprises 34 questions developed to evaluate the presence and severity of NPS in healthy and pre-dementia populations [23]. The symptom is considered present if it represents a change from longstanding behavior and persists for at least 6 months (continuously or intermittently). Individual domains of MBI are: 1) decreased motivation, decreased interest and drive, apathy (which will be further on referred as "decreased motivation"); 2) emotional or affective dysregulation, mood and anxiety symptoms ("emotional dysregulation"); 3) impulse dyscontrol, agitation, aggression, and abnormal reward salience ("impulse dyscontrol"); 4) social inappropriateness, impaired social cognition ("social inappropriateness"); and 5) abnormal thoughts and perception, psychotic symptoms ("psychotic symptoms").

The severity of each present symptom is rated: 1 = mild (noticeable, but not a significant change); 2 = moderate (significant, but not a dramatic change); and 3 = severe (very marked or prominent, a dramatic change). We excluded 156 participants with incomplete data in any of the MBI domains (Supplementary Figure S1). MBI-C has been previously validated using a discretization approach [10, 24, 25]. Thus, we created a binary variable representing MBI syndrome using a cut-off value of more than 8 points ("MBI syndrome"), which has demonstrated good sensitivity and specificity for clinically diagnosed MBI according to the

ISTAART diagnostic criteria in participants with subjective cognitive decline [10], and binary variables indicating the presence of at least one symptom of any severity in an individual MBI domain, which have also been used in previous studies [25].

Cognition

Participants and their informants were dementia-free at enrolment based on self-report. Cognition was measured on a yearly basis using four tests that had been previously adapted and validated for online use: digit span (DS), paired associate learning (PAL), self-ordered search (SOS) and verbal reasoning (VR) [26, 27]. The participants had up to three attempts to complete the same test battery across seven days ensuring a break of 24 hours between sessions. The score of digit span (ranging between 0 and 20), paired associated learning (ranging between 0 and 11) and self-ordered search (ranging between 0 and 20) represents the total number of correct answers. The score of verbal reasoning test (ranging between -1 and 70) is calculated as the total number of trials answered correctly, minus the number answered incorrectly. The final outcome measures were calculated as a mean of the scores from up to the three separate attempts. Cognitive decline was operationalized as an annual decrease in the final scores by including a two-way interaction between time and exposure in longitudinal analysis.

The digit span test is based on the ability to remember a sequence of numbers that appear on the screen one at a time and captures deficits in attention and concentration [28]. The paired associate learning test evaluates episodic memory by presenting a series of objects that are hidden under boxes. Participants are required to remember, which object is hidden under which box. Deficits in paired associate learning have been found to correlate with hippocampal atrophy, which is one of the first neuroimaging features of AD [29]. The self-ordered search

test is based on self-ordered search tasks for assessment of spatial working memory. The task is to find a symbol hidden under an on-screen box and, when found, participants are asked to search for another symbol while remembering that a symbol would not be hidden in the same box twice. Lower scores often indicate frontal lobe damage [30]. The verbal reasoning test is an online adaptation of Baddeley's Gramatical Reasoning test, which correlates well with the ability to reason, analyse and solve problems known as fluid intelligence [31]. Participants are asked to click on "True" or "False" button in order to express whether they agree with a statement describing a relationship between two shapes (a circle, a square, etc.) on the screen.

Covariates

Covariates were selected based on literature as sociodemographic and health-related characteristics associated with MBI and cognition [32]. Sociodemographic characteristics include information on gender/sex (male vs. female), ethnic origin (white vs. non-white), co-habitation status (married/co-habiting vs. living alone), employment status (employed vs. other). Education level was categorized into three groups: low (secondary education); middle (post-secondary education, vocational qualification, undergraduate degree) and high (post-graduate degree, doctorate). Socioeconomic covariates were categorized for the purpose of descriptive analysis, detailed description of covariates used in statistical models is included in the Supplement. Health-related characteristics were self-reported at baseline and include body-mass index (BMI; calculated as weight in kilograms divided by height in meters squared), hypertension, history of heart disease (heart disease, heart attack and/or angina), diabetes and hypercholesterolemia.

Analytical sample

Only participants that had 1) available measures on cognition at baseline and at least 1 follow-up occasion, and 2) informant rated MBI-C assessment at baseline or at year 1, if baseline assessment was not performed, were considered for the present analysis (n = 10,244). To assure that presence of MBI is not attributable to other health conditions, we excluded participants who reported history of stroke (n=149), Parkinson's disease (n=22), mania/bipolar/manic depression (n=48), anxiety/generalized anxiety disorder (n=1 410), social anxiety (n=121), agoraphobia (n=34), panic attacks (n=520), obsessive-compulsive disorder (n=34), anorexia nervosa (n=81), bulimia nervosa (n=54), psychological overeating/binge eating (n=50), schizophrenia (n=5), other psychotic illnesses (n=28), personality disorders (n=13), autism/Asperger's/autistic spectrum disorder (n=13), or attention deficit disorder (n=7). In addition, participants with clinical signs of depression defined by score ≥ 14 at Patient Health Questionnaire-9 scale were also excluded (n=99). This procedure is in accordance with the International Society to Advance Alzheimer's Research and Treatment-Alzheimer's Association (ISTAART-AA) MBI criteria and has been used in previous studies [10, 23]. In total, 2,063 participants were excluded (some participants reported more than one of the above-mentioned conditions), leaving 8,181 persons in the final analytical sample (flowchart presented on Supplementary Figure S1) with median follow-up 3.07 years (interquartile range 2.02- 3.22). Participants with missing data on covariates were kept in the sample for the descriptive analyses.

Statistical analysis

The analysis was performed in two steps. First, we tested whether the association of MBI (syndrome and individual MBI domains) with the level of cognitive performance differs by gender/sex (*cross-sectional analysis*). Second, we studied whether males and females differ in

the association of MBI (syndrome and individual MBI domains) with the rate of cognitive decline (*longitudinal analysis*).

Cross-sectional analysis

Descriptive data of the analytical sample is presented as frequency (n [%]), mean ± standard deviation (SD), or median and interquartile range (IQR). Differences between males and females were tested using independent samples t-test for continuous variables with normal distribution, Mann-Whitney test for continuous variables with skewed distribution and $\chi 2$ test for binary variables. Effect size of the gender/sex difference was calculated as Cohen's d for continuous variables and Cramer's v for categorical variables. Linear regression was applied to estimate beta coefficients with 95% confidence intervals (CIs) for the associations of the independent variable MBI (syndrome and individual MBI domains) with the level of cognitive performance at baseline.

To assess whether gender/sex moderates the association of MBI (syndrome and individual MBI domains) with the level of cognitive performance, we included a two-way interaction term between MBI (syndrome and individual MBI domains) and gender/sex into a model adjusted for age and assessed the interaction effect using likelihood ratio (LR) test. We performed stratified analyses, where appropriate. Three sets of models are presented, stepwise adjusting for covariates. Model 1 is adjusted for age, Model 2 for age and sociodemographic characteristics (employment status, ethnic origin, co-habitation status, education level), Model 3 for age, sociodemographic and health-related characteristics (BMI, hypertension, history of heart disease, diabetes, hypercholesterolemia).

Longitudinal analysis

Methods of linear mixed-effects modelling were applied to explore whether there is an association of MBI (syndrome and individual MBI domains) with the rate of cognitive decline. Participants and time (in years since baseline) were set as random intercepts, time as random slope at participant level, and time, MBI, gender/sex and baseline age (centered around mean) as fixed effects. To assess whether gender/sex moderates the association of MBI with the rate of cognitive decline, we included a three-way interaction term between MBI, time and gender/sex (MBI × time × gender/sex) in Model 1. We performed stratified analyses, where appropriate. We added other covariates as fixed effects in a stepwise approach: sociodemographic characteristics (employment status, ethnic origin, co-habitation status, education level) in Model 2; and health-related characteristics (BMI, hypertension, history of heart disease, diabetes, hypercholesterolemia) in Model 3. In addition, as participants might become familiar with the cognitive test battery when it is administered repeatedly, which could mask cognitive decline, we controlled for practice effect. To select the right method to control for practice effect, we compared three sets of models using different indicators in Model 1: 1) binary indicator of the first test; 2) number of prior tests; and 3) the square root of the number of prior tests [33]. The indicator based on square root of the number of prior tests performed best according to Akaike information criterion and is therefore used in all presented models.

Secondary analysis

We performed two sets of secondary analyses. First, because the prevalence of NPS is lower in younger individuals with AD [34, 35], we assumed the occurrence of MBI might follow the same age group pattern. In addition, recent evidence shows that there is a stronger association between genetic markers and cognitive decline in older age groups [36]. To assess whether there are age differences in the association of MBI with cognitive performance, we tested a three-way interaction of MBI and gender/sex with age group (55-65 vs. 65 and more) and then

we stratified the analysis by age groups and gender/sex, if appropriate. Second, because people with mild cognitive impairment exhibit symptoms of MBI more often than cognitively healthy individuals [37], we repeated the longitudinal analysis on a dataset of a cognitively healthy population (n=7,853 participants). We excluded participants who self-reported mild cognitive impairment (n=15) at baseline and participants with a baseline level of cognitive performance 1.5 or more standard deviations below the average (indicating mild cognitive impairment) on 2 or more cognitive domains (n=325).

As this was an exploratory analysis, we did not control for multiple comparisons and use p value <0.05 as a threshold for statistical significance. All analyses were carried out using Stata software v 16.1.

RESULTS

Out of 8 181 individuals (median age 63 years, 73% females), 11% of females and 14% of males had a score of more than 8 points on MBI-C (p=0.014, V=0.036, Table 1). The average number of MBI symptoms for each participant was 2.84, median (IQR) was 1 (0 - 4). Females and males differed in the proportion of 4 out of 5 individual MBI domains: females exhibited more often symptoms of emotional dysregulation (45% vs. 36% in males; p<0.001), while less often symptoms of decreased motivation (25% vs. 30%; p<0.001), impulse dyscontrol (40% vs. 44%; p=0.001) and social inappropriateness (12% vs. 15%; p<0.001). There were no significant gender/sex differences in frequency of psychotic symptoms. There were gender/sex differences with a small effect size in the baseline scores of all 4 cognitive tests: females scored lower than males in digit span (7.41 vs. 7.54; p=0.001, d=-0.085), paired association learning (4.54 vs. 4.50; p=0.03, d=0.052) and self-ordered search (7.54 vs. 7.88; p<0.001, d=-0.158),

but higher in verbal reasoning (32.69 vs. 31.87; p<0.001, d=0.093). At baseline, males were on average older, more educated, were more frequently married, less commonly employed and had higher prevalence of hypertension, heart disease, diabetes and hypercholesterolemia.

Cross-sectional analysis

We found several associations of MBI with the level of baseline cognitive performance across individual domains in the whole analytical sample (Supplementary Table S1). Gender/sex moderated the association of the MBI syndrome with the level of cognitive performance in paired associate learning (p from LR test 0.035). The MBI syndrome was associated with a lower level of paired associate learning score only in males (B -0.158; 95% CI -0.245 to -0.072; Model 1, Table 2). The association attenuated but remained statistically significant in the fully adjusted model (B -0.154; 95% CI -0.241 to -0.067; Model 3, Table 2). When considering individual MBI domains, gender/sex moderated the association of impulse dyscontrol with the level of cognitive performance in digit span (p from LR test 0.040) and paired associate learning (p from LR test 0.035). When stratified, impulse dyscontrol was associated with a lower level of digit span score only in males (B=-0.229; 95% CI -0.351 to -0.108, Model 1, Table 2) and with paired associate learning score only in males (B=-0.093; 95% CI -0.153 to -0.033, Model 1, Table 2). All associations attenuated but remained significant after adjustment for sociodemographic characteristics in Model 2 (employment status, ethnic origin, co-habitation status, education level) and further adjustment for health-related characteristics in Model 3 (BMI, hypertension, history of heart disease, diabetes, hypercholesterolemia).

Longitudinal analysis

We found an association of the MBI syndrome and all MBI domains with cognitive decline in self-ordered search and verbal reasoning (Supplementary Table S3) in the whole analytical

sample. Gender/sex moderated the association of MBI syndrome as well as all MBI domains with the rate of cognitive decline in verbal reasoning (p from LR test <0.001). When stratified by gender/sex, the MBI syndrome (Supplementary Figure S2), decreased motivation and impulse dyscontrol were related to a higher rate of cognitive decline in verbal reasoning in both genders/sexes, but in all cases to a greater extent in males than females (Table 3). The association of emotional dysregulation with the rate of cognitive decline in verbal reasoning was present exclusively in females (B=-0.175; 95% CI -0.297 to -0.052, Model 1, Table 3), while the association of social inappropriateness (B=-0.298; 95% CI -0.564 to -0.031, Model 1, Table 3) and psychotic symptoms (B=-0.554; 95% CI -0.977 to -0.132, Model 1, Table 3) with a higher rate of cognitive decline was present exclusively in males. These associations attenuated but remained statistically significant in the fully adjusted model.

Secondary analysis

There was a significant interaction (p value from LR test < 0.05) with age group in cognitive performance in paired associate learning. When stratified by age group, the associations found in the cross-sectional analysis were present only in the group of older males (65 years or older, Supplementary Table S2). When the longitudinal analysis was repeated on a sample of cognitively healthy individuals, we obtained results similar to our main findings: significant associations between higher rate of cognitive decline in verbal reasoning and MBI domains were present only in males (Supplementary Table S4 and S5). Specifically, we found these associations in the domain of decreased motivation and psychotic symptoms in all three models.

DISCUSSION

In the present study, we explored gender/sex differences in the association of MBI with cognitive ageing for the first time. Overall, males exhibited symptoms in more domains of MBI than females, particularly decreased motivation, impulse dyscontrol and social inappropriateness. Total MBI-C score and individual domains were associated with cognitive performance and rate of decline in the whole sample. However, when gender/sex differences were present, these associations were present either exclusively in males or to a greater extent in males, with the exception of emotional dysregulation, which was present only in females.

Our results add valuable insights into connections between gender/sex, MBI, and cognition. Mortby et al. reported that males were more likely to exhibit symptoms of decreased motivation and impulse dyscontrol than females [20]. Similarly, apathy, agitation and irritability have been reported more frequently in older males than females in other studies [21, 22]. Given that dementia is a syndrome caused by several distinctive underlying diseases affecting different brain areas, our novel focus on the putative prodromal marker of MBI results suggest that non-cognitive symptoms of dementia may vary by gender/sex even during early manifestation.

A possible explanation of our findings might lie in the entorhinal cortex. Neuropathological changes in entorhinal cortex have been previously linked to impulse dyscontrol, a heterogenous symptom which may refer to agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, or stimulus bind, and is a recognized feature of neurodegenerative disorders [23, 38]. A study based on a sample from the Baltimore Longitudinal Study of Aging shows that males with amyloid pathology, a marker of AD, experience a steeper volumetric decline in entorhinal and parahippocampal regions, thus suggesting that females are more resilient towards volumetric loss in these areas [39]. This hypothesis is supported by recent findings from the Czech Brain Aging Study, which revealed that atrophy in both the entorhinal cortex

and hippocampus is associated with MBI in a group of memory clinic patients with subjective cognitive decline and mild cognitive impairment [38]. In addition, higher tau-PET signal in the entorhinal cortex/hippocampus is associated with higher MBI-C scores in cognitively unimpaired amyloid positive individuals [14]. Another study of neural correlates among cognitively unimpaired individuals and patients with mild behavioral impairment and Alzheimer's disease found that impulse dyscontrol is associated with changes in fornix, superior fronto-occipital fasciculus, cingulum, uncinate fasciculus and lower cortical thickness in the parahippocampal gyrus [40].

However, structural and functional correlates alone might be insufficient to explain the gender/sex differences in the association between MBI symptoms and cognitive decline, as MBI symptoms might reflect differences in brain neurochemistry. Even though gender/sex differences in serotonergic system have not been thoroughly studied in the context of cognitive aging, there is a body of evidence supporting gender/sex differences in serotonin neurotransmission in other psychiatric diagnoses [41]. For example, previous evidence have shown that female sex hormones modulate 5-HT1A receptors, which have been suggested as one of the explanations for higher prevalence of major depressive disorder in females [42]. In addition, previous studies have proposed that genetic variation in the serotonin receptor gene 5-HT2A is associated with the occurrence of hallucinations and delusions in patients with AD [43, 44]. Also, loss of neuroprotective effects of estrogen, such as modulation of neurotransmitter synthesis, synaptic plasticity and mitochondrial activity, related to menopausal changes in women might play a role in differential manifestations of MBI symptoms [45].

Another explanation could be the fact that individual dementia subtypes presenting with different NPS are not equally distributed between genders/sexes. For example, psychotic symptoms affect around 30% of patients with AD in comparison to around 50% of patients with PD dementia and dementia with Lewy bodies (DLB), both of which are more common in males than females [46-48]. Recently, late onset psychiatric symptoms have been proposed as one of the three prototypic prodromal DLB syndromes [49]. In addition, decreased motivation and psychotic symptoms have been found to be strong predictors of disease progression in frontotemporal degeneration (FTD), which appears to be more common in males [50-52]. Moreover, recent findings show that females with behavioral variant of FTD have greater ability to cope with neuropathological changes compared to males and they exhibit less behavioral symptoms, including apathy, despite the same level of atrophy burden [53]. In contrast, progression of AD, in which females account for 60% of patients [3], has been more often linked to the presence of depressive symptoms [52, 54].

Several limitations need to be mentioned. Participants were not representative of the general population of the United Kingdom, as females, individuals with higher education and White people were overrepresented, which might lead to an underestimation of the association in general population. It should be noted that although diagnosis of dementia is an exclusion criterion for participation in the PROTECT study, the diagnosis is based on self-report by the participant. Therefore, it is possible that our sample might include people with early-stage undiagnosed dementia. However, our main results were further supported by results obtained from the secondary analysis, in which we excluded those with self-reported MCI and MCI operationalised by the computerised test scores. Another limitation is that we don't have information on the relationship of the informant or time spent with the participant. Thus, this might affect the recognition of MBI symptoms by the informant and introduce differences

between participants. Next, we performed a large number of statistical tests, which increases the risk of type I error, but most of our comparisons are likely to be correlated. Furthermore, the observed effect sizes are relatively small, but meaningful on a population level. On the contrary, this study is unique as MBI has not been used as a predictor of cognitive decline separately for males and females before. We used a battery of four neuropsychological tests assessing multiple cognitive domains and a validated MBI-C, rather than an algorithm to convert another scale, to find all possible links between MBI and cognition. Even though the follow-up period for a cognitively healthy community dwelling sample is rather short in our study, to our knowledge, it represents the longest and most detailed neuropsychological analysis of MBI to date. Further longitudinal studies with biomarker assessment are required to find out the role of gender/sex in the relationship between MBI symptoms and dementia pathology.

In conclusion, this study provides unique evidence that there are gender/sex differences in the prevalence of MBI symptoms as well as in the association of MBI with the level of cognitive performance and its rate of decline in older adults. Males who exhibit MBI symptoms are at risk of faster cognitive decline than females, particularly when psychotic symptoms and symptoms of decreased motivation occur.

ACKNOWLEDGMENTS

This paper represents independent research coordinated by the University of Exeter and King's College London and is funded in part by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. This research was also supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula and the National Institute for Health Research (NIHR) Exeter Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

The authors were supported by the Ministry of Health of the Czech Republic (Grant NU20J-04-00022; PC, KW), PRIMUS (247066) conducted at Charles University (PC, KW), the "Sustainability for the National Institute of Mental Health" (Grant LO1611), with a financial support from the Ministry of Education, Youth and Sports of the Czech Republic (PC), and by the Czech Alzheimer Endowment Fund (KW).

CONFLICT OF INTERESTS

Dr. Wolfova has nothing to disclose. Dr. Creese has nothing to disclose. Professor Aarsland reports grants and personal fees from Astra-Zeneca, grants and personal fees from H. Lundbeck, grants and personal fees from Novartis Pharmaceuticals, grants and personal fees from GE Health, grants and personal fees from Eisai, and grants and personal fees from Axovant, outside the submitted work. Dr. Ismail reports grants and personal fees from Janssen, personal fees from Lundbeck, personal fees from Sunovion, and personal fees from Otsuka, outside the submitted work. Dr. Corbett has nothing to disclose. Professor Ballard reports grants from Takeda, grants and personal fees from Acadia pharmaceutical company, grants and personal fees from Lundbeck, personal fees from Roche, personal fees from Otsuka, personal fees from Biogen, personal fees from Orion, personal fees from Eli Lilly, personal fees from Novo Nordisk, personal fees from AARP, grants and personal fees from Synexus, and personal fees from Exciva outside the submitted work. Professor Hampshire is owner and director of Future Cognition Ltd, which develops bespoke online cognitive tests for third parties. Dr. Cermakova has nothing to disclose.

REFERENCES

[1] Mielke MM, Vemuri P, Rocca WA (2014) Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol* **6**, 37-48.

[2] Arvanitakis Z, Shah RC, Bennett DA (2019) Diagnosis and Management of Dementia: Review. *Jama* **322**, 1589-1599.

[3] (2014) 2014 Alzheimer's disease facts and figures. *Alzheimers Dement* **10**, e47-92.

[4] Laws KR, Irvine K, Gale TM (2016) Sex differences in cognitive impairment in Alzheimer's disease. *World J Psychiatry* **6**, 54-65.

[5] Podcasy JL, Epperson CN (2016) Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci* **18**, 437-446.

[6] Ferreira L, Ferreira Santos-Galduróz R, Ferri CP, Fernandes Galduróz JC (2014) Rate of cognitive decline in relation to sex after 60 years-of-age: a systematic review. *Geriatr Gerontol Int* **14**, 23-31.

[7] Ferretti MT, Iulita MF, Cavedo E, Chiesa PA, Schumacher Dimech A, Santuccione Chadha A, Baracchi F, Girouard H, Misoch S, Giacobini E, Depypere H, Hampel H, for the Women's Brain P, the Alzheimer Precision Medicine I (2018) Sex differences in Alzheimer disease — the gateway to precision medicine. *Nature Reviews Neurology* **14**, 457-469.

[8] Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, Agüera-Ortiz L, Sweet R, Miller D, Lyketsos CG (2016) Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement* **12**, 195-202.

[9] Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE (2021) Mild Behavioral Impairment and Subjective Cognitive Decline Predict Cognitive and Functional Decline. *J Alzheimers Dis*.

[10] Creese B, Brooker H, Ismail Z, Wesnes KA, Hampshire A, Khan Z, Megalogeni M, Corbett A, Aarsland D, Ballard C (2019) Mild Behavioral Impairment as a Marker of Cognitive Decline in Cognitively Normal Older Adults. *Am J Geriatr Psychiatry* **27**, 823-834.

[11] Burhanullah MH, Tschanz JT, Peters ME, Leoutsakos JM, Matyi J, Lyketsos CG, Nowrangi MA, Rosenberg PB (2020) Neuropsychiatric Symptoms as Risk Factors for Cognitive Decline in Clinically Normal Older Adults: The Cache County Study. *Am J Geriatr Psychiatry* **28**, 64-71.

[12] Leoutsakos JM, Forrester SN, Lyketsos CG, Smith GS (2015) Latent Classes of Neuropsychiatric Symptoms in NACC Controls and Conversion to Mild Cognitive Impairment or Dementia. *J Alzheimers Dis* **48**, 483-493.

[13] Lussier FZ, Pascoal TA, Chamoun M, Therriault J, Tissot C, Savard M, Kang MS, Mathotaarachchi S, Benedet AL, Parsons M, Qureshi MNI, Thomas ÉM, Shin M, Dion L-A, Massarweh G, Soucy J-P, Tsai I-H, Vitali P, Ismail Z, Rosa-Neto P, Gauthier S (2020) Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. *Alzheimer's & Dementia* **16**, 192-199.

[14] Johansson M, Stomrud E, Insel PS, Leuzy A, Johansson PM, Smith R, Ismail Z, Janelidze S, Palmqvist S, van Westen D, Mattsson-Carlgren N, Hansson O (2021) Mild

behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. *Transl Psychiatry* **11**, 76.

[15] Naude JP, Gill S, Hu S, McGirr A, Forkert ND, Monchi O, Stys PK, Smith EE, Ismail Z, for the Alzheimer's Disease Neuroimaging I (2020) Plasma Neurofilament Light: A Marker of Neurodegeneration in Mild Behavioral Impairment. *Journal of Alzheimer's Disease* **76**, 1017-1027.

[16] Miao R, Chen HY, Gill S, Naude J, Smith EE, Ismail Z (2021) Plasma β-Amyloid in Mild Behavioural Impairment - Neuropsychiatric Symptoms on the Alzheimer's Continuum. *J Geriatr Psychiatry Neurol*, 8919887211016068.

[17] Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT (2009) Predictors of neuropsychiatric symptoms in nursing home patients: influence of gender and dementia severity. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences* **24**, 1079-1086.

[18] Ropacki SA, Jeste DV (2005) Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *American Journal of Psychiatry* **162**, 2022-2030.

[19] Lee J, Lee KJ, Kim H (2017) Gender differences in behavioral and psychological symptoms of patients with Alzheimer's disease. *Asian J Psychiatr* **26**, 124-128.

[20] Mortby ME, Ismail Z, Anstey KJ (2018) Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. *International Psychogeriatrics* **30**, 221-232.

[21] Geda YE, Roberts RO, Mielke MM, Knopman DS, Christianson TJ, Pankratz VS, Boeve BF, Sochor O, Tangalos EG, Petersen RC, Rocca WA (2014) Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. *Am J Psychiatry* **171**, 572-581.

[22] Hölttä EH, Laakkonen ML, Laurila JV, Strandberg TE, Tilvis RS, Pitkälä KH (2012) Apathy: prevalence, associated factors, and prognostic value among frail, older inpatients. *J Am Med Dir Assoc* **13**, 541-545.

[23] Ismail Z, Agüera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, Gauthier S, Geda YE, Herrmann N, Kanji J, Lanctôt KL, Miller DS, Mortby ME, Onyike CU, Rosenberg PB, Smith EE, Smith GS, Sultzer DL, Lyketsos C (2017) The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *J Alzheimers Dis* **56**, 929-938.

[24] Kassam F, Chen H, Nosheny RL, McGirr A, Williams T, Ng N, Camacho M, Mackin RS, Weiner MW, Ismail Z (2022) Cognitive profile of people with mild behavioral impairment in Brain Health Registry participants. *International Psychogeriatrics*, 1-10.

[25] Creese B, Griffiths A, Brooker H, Corbett A, Aarsland D, Ballard C, Ismail Z (2020) Profile of mild behavioral impairment and factor structure of the Mild Behavioral Impairment Checklist in cognitively normal older adults. *Int Psychogeriatr* **32**, 705-717.

[26] Owen AM, Hampshire A, Grahn JA, Stenton R, Dajani S, Burns AS, Howard RJ, Ballard CG (2010) Putting brain training to the test. *Nature* **465**, 775-778.

[27] Wesnes KA, Brooker H, Ballard C, McCambridge L, Stenton R, Corbett A (2017) Utility, reliability, sensitivity and validity of an online test system designed to monitor changes in cognitive function in clinical trials. *Int J Geriatr Psychiatry* **32**, e83-e92.

[28] Hebben Nancy et al. (2002) *Essentials of Neuropsychological Assessment,*, John Wiley & Sons, Incorporated.
[29] Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ (1995) Computerized delayed matching to sample and paired associate performance in the early detection of dementia. *Appl Neuropsychol* **2**, 72-78.
[30] Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW (1990) Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**, 1021-1034.
[31] Baddeley AD (1968) A 3 min reasoning test based on grammatical transformation. *Psychonomic Science* **10**, 341-342.
[32] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* **396**, 413-446.
[33] Vivot A, Power MC, Glymour MM, Mayeda ER, Benitez A, Spiro A, 3rd, Manly JJ, Proust-Lima C, Dufouil C, Gross AL (2016) Jump, Hop, or Skip: Modeling Practice Effects in Studies of Determinants of Cognitive Change in Older Adults. *Am J Epidemiol* **183**, 302-314.
[34] Zhao Q-F, Tan L, Wang H-F, Jiang T, Tan M-S, Tan L, Xu W, Li J-Q, Wang J, Lai T-J, Yu J-T (2016) The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders* **190**, 264-271.
[35] van Vliet D, de Vugt ME, Aalten P, Bakker C, Pijnenburg YAL, Vernooij-Dassen MJFJ, Koopmans RTCM, Verhey FRJ (2012) Prevalence of Neuropsychiatric Symptoms in Young-Onset Compared to Late-Onset Alzheimer's Disease – Part 1: Findings of the Two-Year Longitudinal NeedYD-Study. *Dementia and Geriatric Cognitive Disorders* **34**, 319-327.
[36] Creese B, Arathimos R, Brooker H, Aarsland D, Corbett A, Lewis C, Ballard C, Ismail Z (2021) Genetic risk for Alzheimer's disease, cognition, and mild behavioral impairment in healthy older adults. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* **13**, e12164.
[37] Rouse HJ, Small BJ, Schinka JA, Loewenstein DA, Duara R, Potter H (2020) Mild behavioral impairment as a predictor of cognitive functioning in older adults. *Int Psychogeriatr*, 1-9.
[38] Matuskova V, Ismail Z, Nikolai T, Markova H, Cechova K, Nedelska Z, Laczo J, Wang M, Hort J, Vyhnalek M (2021) Mild behavioral impairment is associated with atrophy of entorhinal cortex and hippocampus in a memory clinic cohort. *Frontiers in Aging Neuroscience*.
[39] Armstrong NM, Huang CW, Williams OA, Bilgel M, An Y, Doshi J, Erus G, Davatzikos C, Wong DF, Ferrucci L, Resnick SM (2019) Sex differences in the association between amyloid and longitudinal brain volume change in cognitively normal older adults. *Neuroimage Clin* **22**, 101769.
[40] Gill S, Wang M, Mouches P, Rajashekar D, Sajobi T, MacMaster FP, Smith EE, Forkert ND, Ismail Z (2021) Neural correlates of the impulse dyscontrol domain of mild behavioral impairment. *Int J Geriatr Psychiatry*.

[41] Cosgrove KP, Mazure CM, Staley JK (2007) Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biol Psychiatry* **62**, 847-855.
[42] Kaufman J, DeLorenzo C, Choudhury S, Parsey RV (2016) The 5-HT1A receptor in Major Depressive Disorder. *Eur Neuropsychopharmacol* **26**, 397-410.
[43] Tang L, Wang Y, Chen Y, Chen L, Zheng S, Bao M, Xiang J, Luo H, Li J, Li Y (2017) The Association between 5HT2A T102C and Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease: A Meta-Analysis. *Biomed Res Int* **2017**, 5320135.
[44] Burstein ES (2021) Relevance of 5-HT(2A) Receptor Modulation of Pyramidal Cell Excitability for Dementia-Related Psychosis: Implications for Pharmacotherapy. *CNS Drugs* **35**, 727-741.
[45] Conde DM, Verdade RC, Valadares ALR, Mella LFB, Pedro AO, Costa-Paiva L (2021) Menopause and cognitive impairment: A narrative review of current knowledge. *World J Psychiatry* **11**, 412-428.
[46] Gallagher D, Fischer CE, Iaboni A (2017) Neuropsychiatric Symptoms in Mild Cognitive Impairment. *Can J Psychiatry* **62**, 161-169.
[47] Nelson PT, Schmitt FA, Jicha GA, Kryscio RJ, Abner EL, Smith CD, Van Eldik LJ, Markesbery WR (2010) Association between male gender and cortical Lewy body pathology in large autopsy series. *J Neurol* **257**, 1875-1881.
[48] Smith KM, Dahodwala N (2014) Sex differences in Parkinson's disease and other movement disorders. *Exp Neurol* **259**, 44-56.
[49] McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, Kantarci K, Muscio C, O'Brien JT, Postuma RB, Aarsland D, Ballard C, Bonanni L, Donaghy P, Emre M, Galvin JE, Galasko D, Goldman JG, Gomperts SN, Honig LS, Ikeda M, Leverenz JB, Lewis SJG, Marder KS, Masellis M, Salmon DP, Taylor JP, Tsuang DW, Walker Z, Tiraboschi P (2020) Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology* **94**, 743-755.
[50] de Boer SCM, Riedl L, van der Lee SJ, Otto M, Anderl-Straub S, Landin-Romero R, Sorrentino F, Fieldhouse JLP, Reus LM, Vacaflor B, Halliday G, Galimberti D, Diehl-Schmid J, Ducharme S, Piguet O, Pijnenburg YAL (2021) Differences in Sex Distribution Between Genetic and Sporadic Frontotemporal Dementia. *J Alzheimers Dis* **84**, 1153-1161.
[51] Ranasinghe KG, Rankin KP, Lobach IV, Kramer JH, Sturm VE, Bettcher BM, Possin K, Christine You S, Lamarre AK, Shany-Ur T, Stephens ML, Perry DC, Lee SE, Miller ZA, Gorno-Tempini ML, Rosen HJ, Boxer A, Seeley WW, Rabinovici GD, Vossel KA, Miller BL (2016) Cognition and neuropsychiatry in behavioral variant frontotemporal dementia by disease stage. *Neurology* **86**, 600-610.
[52] Santacruz Escudero JM, Beltrán J, Palacios Á, Chimbí CM, Matallana D, Reyes P, Perez-Sola V, Santamaría-García H (2019) Neuropsychiatric Symptoms as Predictors of Clinical Course in Neurodegeneration. A Longitudinal Study. *Front Aging Neurosci* **11**, 176.
[53] Illán-Gala I, Casaletto KB, Borrego-Écija S, Arenaza-Urquijo EM, Wolf A, Cobigo Y, Goh SYM, Staffaroni AM, Alcolea D, Fortea J, Blesa R, Clarimon J, Iulita MF, Brugulat-Serrat A, Lladó A, Grinberg LT, Possin K, Rankin KP, Kramer JH, Rabinovici GD, Boxer A, Seeley WW, Sturm VE, Gorno-Tempini ML, Miller BL, Sánchez-Valle R, Perry DC, Lleó A, Rosen HJ Sex differences in the behavioral variant of frontotemporal dementia: A new window to executive and behavioral reserve. *Alzheimer's & Dementia* **n/a**.

[54] Desai R, Charlesworth GM, Brooker HJ, Potts HWW, Corbett A, Aarsland D, Ballard CG (2020) Temporal Relationship Between Depressive Symptoms and Cognition in Mid and Late Life: A Longitudinal Cohort Study. *J Am Med Dir Assoc* **21**, 1108-1113.

TABLES

Table 1 Gender/sex differences in baseline characteristics

	Females (n=5,970, 73.0%)	**Males (n= 2,211, 27.0%)**	**p value[a]**	**Effect size[b]**
Age, median (IQR)	61.8 (56.9–66.8)	64.8 (59.5–69.5)	<0.001	-0.370
White ethnic origin, n (%)	5 569 (93.3)	2 089 (94.5)	0.041	-0.022
Married/co-habiting, n (%)	4 603 (77.1)	1 979 (89.6)	<0.001	-0.139
Education level, n (%)			<0.001	0.054
Low	755 (12.65)	286 (12.9)		
Middle	3 963 (66.4)	1 354 (61.3)		
High	1 252 (21.0)	570 (25.8)		
Employed, n (%)	2 506 (42.0)	799 (36.2)	<0.001	0.053
Cognition				
Digit span, mean ± SD	7.41 ± 1.48	7.54 ± 1.45	0.001	-0.085
Paired associate learning, mean ± SD	4.54 ± 0.76	4.50 ± 0.74	0.031	0.052
Verbal reasoning, mean ± SD	32.70 ± 8.98	31.87 ± 8.70	<0.001	0.093
Spatial working memory, mean ± SD	7.55 ± 2.04	7.88 ± 2.26	<0.001	-0.158
MBI				
MBI syndrome (< 8 points), n (%)	656 (10.99)	300 (13.57)	0.001	0.036
Decreased motivation, n (%)	1 508 (25.26)	669 (30.26)	<0.001	0.050
Emotional dysregulation, n (%)	2 701 (44.8)	797 (35.6)	<0.001	-0.082
Impulse dyscontrol, n (%)	2 350 (39.36)	962 (43.51)	0.001	0.038
Social inappropriateness, n (%)	704 (11.79)	336 (15.20)	<0.001	0.045
Psychotic symptoms, n (%)	405 (6.78)	127 (5.74)	0.090	-0.018
BMI, median (IQR)	24.2 (22.1–27.3)	25.3 (23.2–27.8)	<0.001	-0.152
Comorbidities				
Hypertension, n (%)	1 420 (23.85)	741 (33.71)	<0.001	0.099

Heart disease, n (%)	160 (2.7)	184 (8.4)	<0.001	0.126
Diabetes, n (%)	135 (2.3)	117 (5.3)	<0.001	0.078
Hypercholesterolemia, n (%)	211 (3.5)	122 (5.6)	<0.001	0.045

Note. SD, standard deviation; IQR, interquartile range; MBI, mild behavioral impairment; BMI, body-mass index.

[a] t-test for continuous variables with normal distribution, Mann-Whitney-Wilcoxon test for continuous variables with skewed distribution or chi-square test for categorical variables

[b] effect size of the gender/sex difference is presented as Cohen's d for continuous variables and Cramer's v for categorical variables

Table 2 Association of mild behavioral impairment with the level of cognitive performance, stratified by gender/sex

	B (95% CI)			
	Digit span		**Paired associate learning**	
	Females	**Males**	**Females**	**Males**
MBI syndrome				
Model 1	-	-	-0.036 (-0.096; 0.024)	-0.158 (-0.245; -0.072)***
Model 2	-	-	-0.029 (-0.089; 0.032)	-0.153 (-0.240; -0.066)***
Model 3	-	-	-0.023 (-0.084; 0.038)	-0.154 (-0.241; -0.067)***
Impulse dyscontrol				
Model 1	-0.074 (-0.150; 0.003)	-0.229 (-0.351; -0.108)***	-0.019 (-0.058; 0.020)	-0.093 (-0.153; -0.033)**
Model 2	-0.066 (-0.143; 0.011)	-0.200 (-0.321; -0.078)**	-0.016 (-0.055; 0.023)	-0.080 (-0.141; -0.020)**
Model 3	-0.061 (-0.138; 0.016)	-0.200 (-0.321; -0.080)**	-0.014 (-0.053; 0.024)	-0.080 (-0.140; -0.019) **

Note. CI, confidence interval; MBI, mild behavioral impairment

Model 1: baseline age

Model 2: baseline age, employment status, ethnic origin, co-habitation status, education level

Model 3: baseline age, employment status, ethnic origin, co-habitation status, education level, body-mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

*** $p<0.001$ ** $p<0.01$ * $p<0.05$;

Table 3 Association of mild behavioral impairment with the rate of decline in verbal reasoning, stratified by gender/sex

	B (95% CI)	
	Verbal reasoning	
	Females	**Males**
MBI syndrome		
Model 1	-0.282 (-0.479; -0.084)**	-0.324 (-0.604; -0.045)*
Model 2	-0.282 (-0.479; -0.084)**	-0.325 (-0.604; -0.046)*
Model 3	-0.273 (-0.472; -0.074) **	-0.323 (-0.602; -0.043)*
Emotional dysregulation		
Model 1	-0.175 (-0.297; -0.052)**	-0.178 (-0.376; 0.021)
Model 2	-0.175 (-0.297; -0.052)**	-0.176 (-0.375; 0.022)
Model 3	-0.172 (-0.295; -0.049)**	-0.177 (-0.376; 0.022)
Decreased motivation		
Model 1	-0.229 (-0.371; -0.088)**	-0.334 (-0.541; -0.127)**
Model 2	-0.231 (-0.372; -0.090)**	-0.334 (-0.541; -0.128)**
Model 3	-0.223 (-0.364; -0.081)**	-0.335 (-0.542; -0.128)**
Impulse dyscontrol		
Model 1	-0.135 (-0.260; -0.010)*	-0.216 (-0.407; -0.024)*
Model 2	-0.135 (-0.260; -0.011)*	-0.216 (-0.407; -0.024)*
Model 3	-0.133 (-0.259; -0.008)*	-0.211 (-0.403; -0.019)*
Social inappropriateness		
Model 1	-0.188 (-0.378; 0.003)	-0.298 (-0.564; -0.031)*
Model 2	-0.190 (-0.380; 0.001)	-0.297 (-0.563; -0.031)*
Model 3	-0.186 (-0.378; 0.005)	-0.283 (-0.550; -0.016)*
Psychotic symptoms		
Model 1	-0.160 (-0.408; 0.087)	-0.554 (-0.977; -0.132)*
Model 2	-0.159 (-0.406; 0.088)	-0.557 (-0.978; -0.135)**
Model 3	-0.143 (-0.392; 0.106)	-0.553 (-0.976; -0.131)*

Note. CI, confidence interval; MBI, mild behavioral impairment.

Model 1: baseline age, practice effect

Model 2: baseline age, practice effect, employment status, ethnic origin, co-habitation status, education level

Model 3: baseline age, practice effect, employment status, ethnic origin, co-habitation status, education level, body-mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

*** $p<0.001$ ** $p<0.01$ * $p<0.05$

SUPPLEMENTARY MATERIAL

Description of covariates

Ethnic origin

Participants were asked "What is your ethnic origin?" and were offered the following options: White: English / Welsh / Scottish / Northern Irish / British, White: Irish; White: Gypsy or Irish Traveller; White: European; White: Non-European; Mixed: White and Black Caribbean; Mixed: White and Black African; Mixed: White and Asian; Mixed: Any other Mixed / Multiple ethnic background; Asian / Asian British: Indian; Asian / Asian British: Pakistani; Asian / Asian British: Bangladeshi; Asian / Asian British: Chinese; Asian / Asian British: Any other Asian background; Black / African / Caribbean / Black British: African; Black / African / Caribbean / Black British: Caribbean; Any other Black / African / Caribbean background; Other ethnic group: Arab; Any other ethnic group.

Employment status

Participants were asked "What is your current employment status?" and were offered the following options: Employed (full time); Employed (part time); Self-employed, Retired; Unemployed.

Marital status

Participants were asked "What is your marital status?" and were offered the following options: Married; Widowed; Separated; Divorced; Civil Partnership; Co-habiting; Single.

Education

Participants were asked "What is the highest level of education you have completed?" and were offered the following options: Secondary Education (GCSE/O-Levels); Post-Secondary Education (College, A-Levels, NVQ3 or below, or similar); Vocational Qualification (Diploma, Certificate, BTEC, NVQ 4

and above, or similar); Undergraduate Degree (BA, BSc etc.); Post-graduate Degree (MA, MSc etc.); Doctorate (PhD).

BMI

Participants were asked "What is your height?" and "What is your current weight?". BMI was calculated as weight in kilograms divided by height in meters squared.

Hypertension

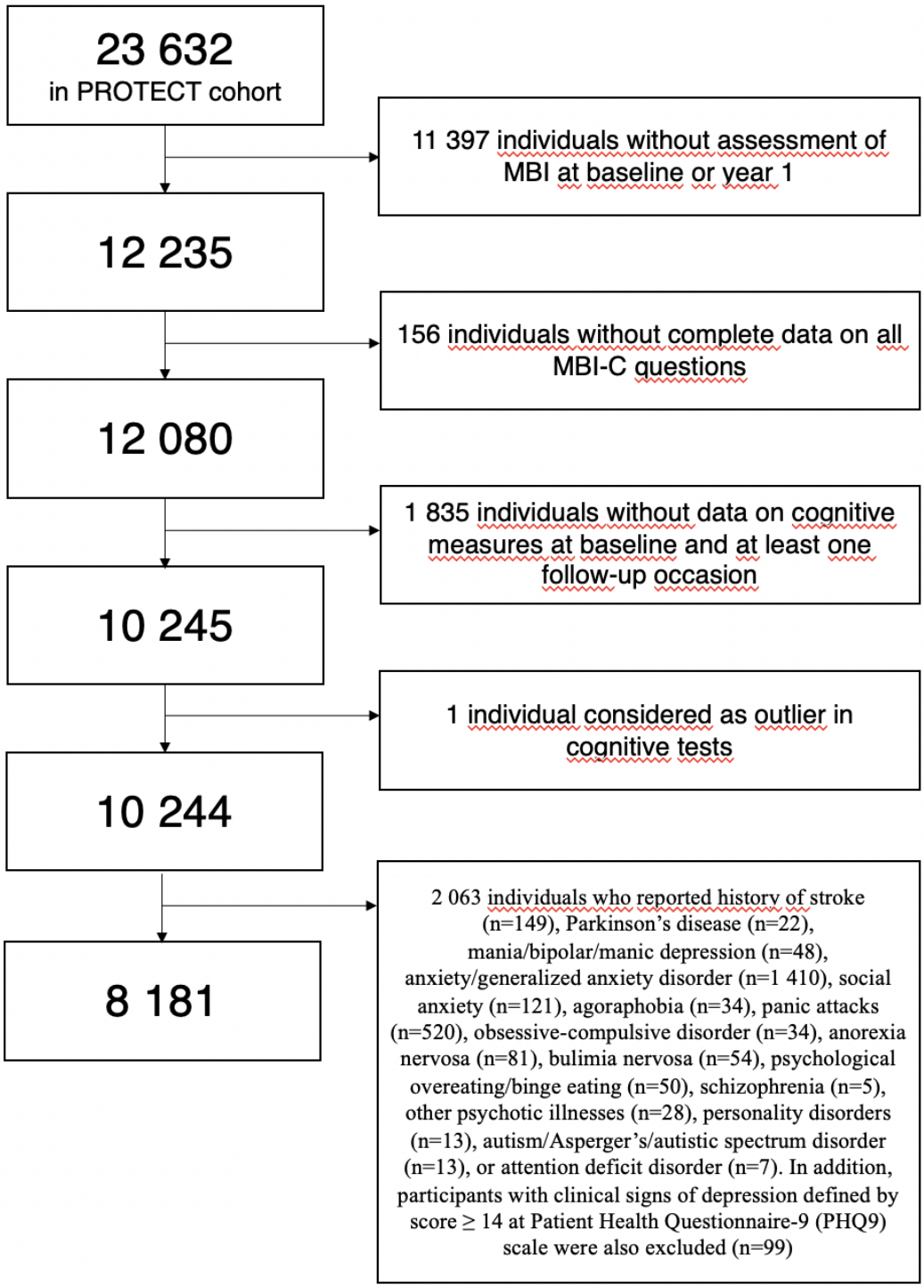
Participants were asked "Has a doctor ever given you a diagnosis of, or told you that you have, any of the following?:" and were offered to answer "High blood pressure" as one of the options.

Heart disease

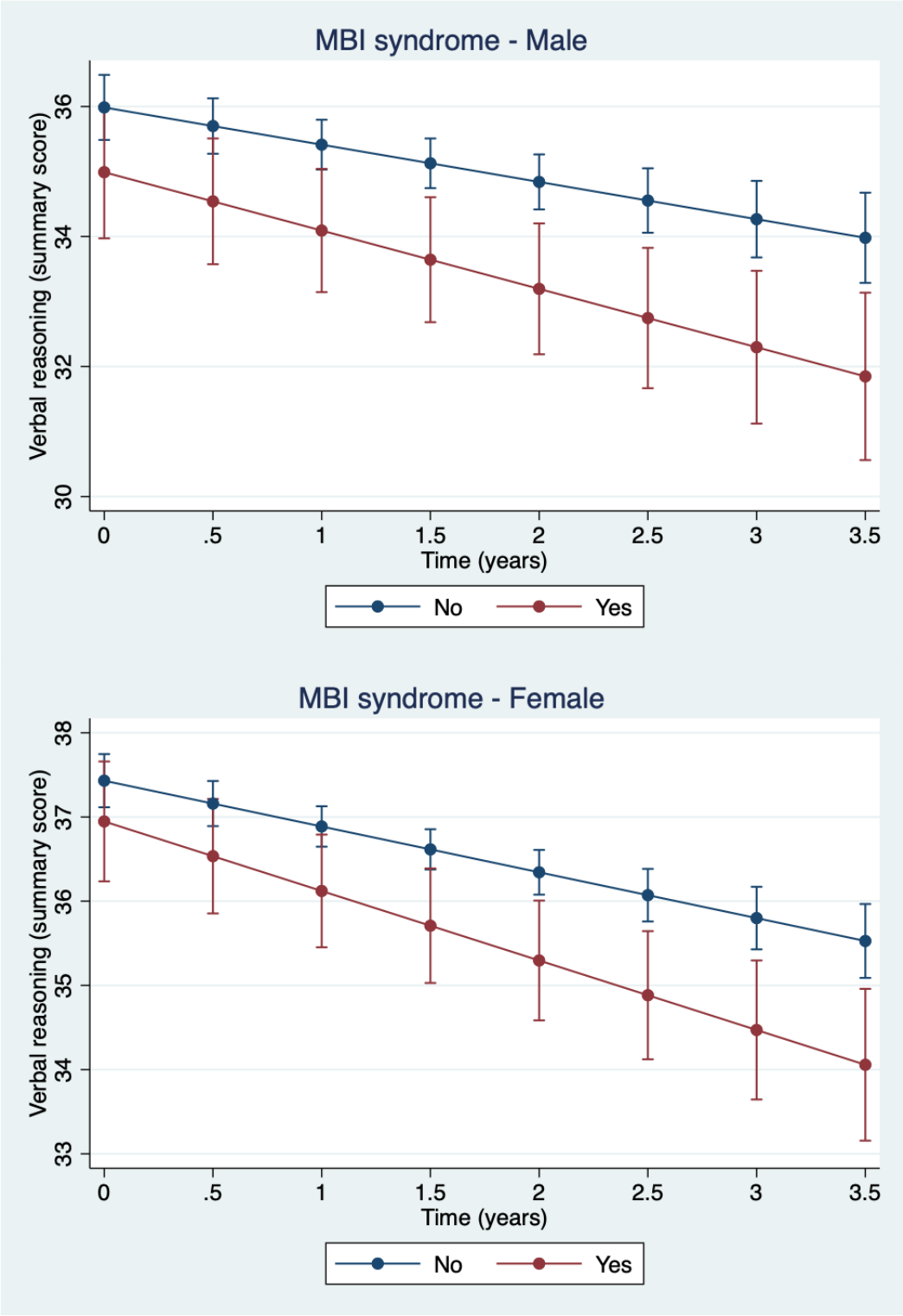
Participants were asked "Has a doctor ever given you a diagnosis of, or told you that you have, any of the following?:" and were offered to answer "Heart disease / Heart attack / Angina" as one of the options.

Diabetes

Participants were asked "Has a doctor ever given you a diagnosis of, or told you that you have, any of the following?:" and were offered to answer "Diabetes" as one of the options.



Supplementary Figure S1 Selection of participants



Supplementary Figure S2 Predictive margins of MBI stratified by gender/sex, Model 1

Supplementary Table S1 Association of MBI with cognitive performance in the whole analytical sample

	B (95% CI)			
	Digit span	**Paired associate learning**	**Self-ordered search**	**Verbal reasoning**
MBI syndrome				
Model 1	-0.100 (-0.199; -0.001)*	-0.074 (-0.124; -0.025)**	-0.163 (-0.302; -0.023)*	-0.508 (-1.088; 0.073)
Model 2	-0.078 (-0.177; 0.021)	-0.068 (-0.117; -0.018)**	-0.138 (-0.278; 0.001)	-0.197 (-0.762; 0.367)
Model 3	-0.082 (-0.181; 0.018)	-0.064 (-0.114; -0.014)*	-0.125 (-0.265; 0.015)	-0.160 (-0.729; 0.410)
Emotional dysregulation				
Model 1	-0.150 (-0.215; -0.086)***	-0.055 (-0.087; -0.023)***	-0.163 (-0.254; -0.072)***	-0.257 (-0.636; 0.122)
Model 2	-0.146 (-0.211; -0.082)***	-0.054 (-0.087; -0.022)***	-0.151 (-0.242; -0.060)**	-0.205 (-0.574; 0.164)
Model 3	-0.140 (-0.205; -0.076)***	-0.051 (-0.084; -0.019)**	-0.146 (-0.237; -0.054)**	-0.197 (-0.567; 0.174)
Decreased motivation				
Model 1	-0.156 (-0.228; -0.084)***	-0.021 (-0.057; 0.015)	-0.077 (-0.179; 0.024)	-0.035 (-0.387; 0.458)
Model 2	-0.140 (-0.212; -0.068)***	-0.015 (-0.051; 0.021)	-0.060 (-0.161; 0.042)	0.227 (-0.184; 0.639)
Model 3	-0.137 (-0.209; -0.065)***	-0.014 (-0.050; 0.022)	-0.043 (-0.145; 0.059)	0.234 (-0.181; 0.648)
Impulse dyscontrol				
Model 1	-0.116 (-0.180; -0.051)***	-0.040 (-0.073; -0.008)*	-0.112 (-0.204; -0.021)*	-0.437 (-0.817; -0.057)*
Model 2	-0.102 (-0.167; -0.037)**	-0.036 (-0.068; -0.003)*	-0.098 (-0.189; -0.007)*	-0.228 (-0.598; 0.142)

Model 3	-0.100 (-0.165; -0.035)**	-0.034 (-0.067; -0.001)*	-0.091 (-0.183; 0.001)	-0.219 (-0.590; 0.153)
Social inappropriateness				
Model 1	-0.082 (-0.177; 0.014)	-0.043 (-0.091; 0.005)	-0.085 (-0.220; 0.049)	-0.628 (-1.189; -0.067)*
Model 2	-0.066 (-0.162; 0.029)	-0.037 (-0.085; 0.011)	-0.065 (-0.200; 0.070)	-0.408 (-0.954; 0.138)
Model 3	-0.070 (-0.165; 0.026)	-0.040 (-0.088; 0.009)	-0.074 (-0.210; 0.061)	-0.427 (-0.976; 0.121)
Psychotic symptoms				
Model 1	-0.157 (-0.286; -0.028)*	-0.080 (-0.144; -0.015)*	-0.181 (-0.363; 0.000)	-0.880 (-1.636; -0.124)*
Model 2	-0.133 (-0.262; -0.004)*	-0.067 (-0.132; -0.003)*	-0.138 (-0.320; 0.044)	-0.537 (-1.273; 0.200)
Model 3	-0.129 (-0.258; 0.000)	-0.064 (-0.129; -0.001)	-0.140 (-0.322; -0.043)	-0.563 (-1.303; 0.178)

Note. B, beta; CI, confidence interval; MBI, mild behavioral impairment

Model 1: baseline age, gender/sex

Model 2: baseline age, gender/sex, employment status, ethnic origin, co-habitation status, education level

Model 3: baseline age, gender/sex, employment status, ethnic origin, co-habitation status, education level, body-mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

*** $p<0.001$ ** $p<0.01$ * $p<0.05$

Supplementary Table S2 Association of mild behavioral impairment with the level of cognitive performance, stratified by gender/sex and age group

	B (95% CI)	
	Paired associate learning	
	Females	**Males**
55-64		
MBI syndrome		
Model 1	-0.076 (-0.150; -0.003)*	-0.086 (-0.207; 0.035)
Model 2	-0.067 (-0.141; 0.007)	-0.079 (-0.202; 0.045)
Model 3	-0.058 (-0.133; 0.017)	-0.086 (-0.211; 0.038)
Impulse dyscontrol		
Model 1	-0.044 (-0.092; 0.003)	-0.059 (-0.143; 0.025)
Model 2	-0.040 (-0.087; 0.008)	-0.054 (-0.139; 0.030)
Model 3	-0.038 (-0.085; 0.010)	-0.054 (-0.139; 0.032)
≥ 65		
MBI syndrome		
Model 1	0.051 (-0.054; 0.155)	-0.232 (-0.355; -0.108)***
Model 2	0.060 (-0.045; 0.165)	-0.228 (-0.352; -0.104)***
Model 3	0.059 (-0.048; 0.165)	-0.220 (-0.345; -0.096)***
Impulse dyscontrol		
Model 1	0.035 (-0.032; 0.101)	-0.134 (-0.220; -0.048)**
Model 2	0.040 (-0.026; 0.107)	-0.119 (-0.206; -0.032)**
Model 3	0.042 (-0.025; 0.109)	-0.118 (-0.206; -0.031)**

Note. CI, confidence interval; MBI, mild behavioral impairment

Model 1: baseline age

Model 2: baseline age, employment status, ethnic origin, co-habitation status, education level

Model 3: baseline age, employment status, ethnic origin, co-habitation status, education level, body-mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

*** $p<0.001$ ** $p<0.01$ * $p<0.05$

Supplementary Table S3 Association of MBI with the rate of cognitive decline in the whole analytical sample

	B (95% CI)			
	Digit span	**Paired associate learning**	**Self-ordered search**	**Verbal reasoning**
MBI syndrome				
Model 1	-0.028 (-0.056; 0.000)*	0.001 (-0.020; 0.021)	-0.079 (-0.131; -0.027)**	-0.318 (-0.480; -0.155)***
Model 2	-0.028 (-0.056; 0.000)*	0.001 (-0.020; 0.021)	-0.078 (-0.130; -0.027)**	-0.318 (-0.480; -0.156)***
Model 3	-0.027 (-0.055; 0.001)	-0.004 (-0.024; 0.017)	-0.079 (-0.131; -0.027)**	-0.313 (-0.477; -0.150)***
Emotional dysregulation				
Model 1	0.000 (-0.018; 0.018)	-0.004 (-0.017; 0.009)	-0.049 (-0.082; -0.016)**	-0.145 (-0.250; -0.041)**
Model 2	0.001 (-0.017; 0.019)	-0.004 (-0.017; 0.009)	-0.048 (-0.082; -0.015)**	-0.145 (-0.249; -0.040)**
Model 3	0.001 (-0.017; 0.019)	-0.005 (-0.018; 0.008)	-0.048 (-0.081; -0.015)**	-0.143 (-0.248; -0.038)**
Decreased motivation				
Model 1	0.002 (-0.018; 0.022)	-0.007 (-0.022; 0.008)	-0.068 (-0.105; -0.030)***	-0.283 (-0.400; -0.166)***
Model 2	0.002 (-0.018; 0.022)	-0.007 (-0.022; 0.008)	-0.068 (-0.106; -0.031)***	-0.284 (-0.401; -0.167)***
Model 3	0.001 (-0.019; 0.021)	-0.009 (-0.024; 0.006)	-0.071 (-0.108; -0.033)***	-0.280 (-0.398; -0.163)***
Impulse dyscontrol				
Model 1	0.004 (-0.014; 0.022)	-0.006 (-0.020; 0.007)	-0.064 (-0.098; -0.031)***	-0.174 (-0.279; -0.069)**
Model 2	0.004 (-0.014; 0.022)	-0.006 (-0.020; 0.007)	-0.064 (-0.098; -0.030) ***	-0.174 (-0.279; -0.069)**

Model 3	0.004 (-0.014; 0.022)	-0.007 (-0.021; 0.006)	-0.063 (-0.096; -0.029)***	-0.171 (-0.277; -0.066)**
Social inappropriateness				
Model 1	0.000 (-0.027; 0.026)	-0.019 (-0.039; 0.001)	-0.066 (-0.116; -0.017)**	-0.249 (-0.405; -0.092)**
Model 2	-0.001 (-0.028; 0.026)	-0.019 (-0.039; 0.001)	-0.067 (-0.117; -0.017)**	-0.250 (-0.406; -0.094)**
Model 3	0.003 (-0.024; 0.029)	-0.018 (-0.037; 0.002)	-0.063 (-0.113; -0.013)*	-0.243 (-0.400; -0.086)**
Psychotic symptoms				
Model 1	0.008 (-0.029; 0.045)	-0.000 (-0.027; 0.027)	0.021 (-0.048; 0.090)	-0.236 (-0.451; -0.022)*
Model 2	0.008 (-0.029; 0.045)	-0.000 (-0.028; 0.027)	0.020 (-0.048; 0.089)	-0.236 (-0.450; -0.022)*
Model 3	0.008 (-0.029; 0.045)	-0.002 (-0.029; 0.025)	0.024 (-0.045; 0.093)	-0.225 (-0.440; -0.010)*

Note. B, beta; CI, confidence interval; MBI, mild behavioral impairment.

Model 1: baseline age, gender/sex, practice effect

Model 2: baseline age, gender/sex, practice effect, employment status, ethnic origin, co-habitation status, education level

Model 3: baseline age, gender/sex, practice effect, employment status, ethnic origin, co-habitation status, education level, body-mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

*** $p<0.001$ ** $p<0.01$ * $p<0.05$

Supplementary Table S4 Association of MBI with the rate of cognitive decline in cognitively healthy analytical sample

	B (95% CI)			
	Digit span	**Paired associate learning**	**Self-ordered search**	**Verbal reasoning**
MBI syndrome				
Model 1	-0.029 (-0.058; -0.001) *	0.003 (-0.018; 0.024)	-0.083 (-0.136; -0.030)**	-0.315 (-0.481; -0.150) ***
Model 2	-0.029 (-0.058; -0.001) *	0.003 (-0.018; 0.024)	-0.083 (-0.135; -0.030)**	-0.316 (-0.481; -0.151) ***
Model 3	-0.028 (-0.056; 0.000)	-0.002 (-0.022; 0.019)	-0.083 (-0.136; -0.030)**	-0.311 (-0.477; -0.145) ***
Emotional dysregulation				
Model 1	-0.003 (-0.021; 0.015)	-0.005 (-0.018; 0.009)	-0.052 (-0.086; -0.019)**	-0.143 (-0.249; -0.037)**
Model 2	-0.003 (-0.021; 0.015)	-0.004 (-0.018; 0.009)	-0.052 (-0.085; -0.018)**	-0.143 (-0.249; -0.037)**
Model 3	-0.002 (-0.020; 0.016)	-0.006 (-0.019; 0.008)	-0.051 (-0.085; -0.017)**	-0.140 (-0.247; -0.034)**
Decreased motivation				
Model 1	0.001 (-0.020; 0.021)	-0.005 (-0.020; 0.010)	-0.063 (-0.101; -0.025)**	-0.278 (-0.397; -0.159)***
Model 2	0.001 (-0.020; 0.021)	-0.005 (-0.020; 0.010)	-0.064 (-0.101; -0.026)***	-0.279 (-0.398; -0.160)***
Model 3	0.000 (-0.020; 0.021)	-0.007 (-0.022; 0.008)	-0.066 (-0.103; -0.028)***	-0.275 (-0.394; -0.155)***
Impulse dyscontrol				
Model 1	0.000 (-0.019; 0.018)	-0.008 (-0.022; 0.005)	-0.070 (-0.104; -0.036)***	-0.166 (-0.273; -0.059)**

Model 2	0.000 (-0.018; 0.018)	-0.008 (-0.022; 0.005)	-0.070 (-0.103; -0.036)***	-0.166 (-0.272; -0.059)**
Model 3	0.000 (-0.019; 0.018)	-0.009 (-0.023; 0.004)	-0.069 (-0.102; -0.035)***	-0.163 (-0.270; -0.056)**
Social inappropriateness				
Model 1	-0.002 (-0.029; 0.025)	-0.016 (-0.036; 0.004)	-0.063 (-0.113; -0.012)*	-0.265 (-0.423; -0.107)**
Model 2	-0.002 (-0.029; 0.025)	-0.016 (-0.036; 0.004)	-0.063 (-0.113; -0.013)*	-0.265 (-0.423; -0.107)***
Model 3	0.001 (-0.026; 0.028)	-0.014 (-0.034; 0.006)	-0.059 (-0.109; -0.009)*	-0.259 (-0.417; -0.100)**
Psychotic symptoms				
Model 1	0.003 (-0.035; 0.040)	-0.007 (-0.035; 0.020)	0.029 (-0.040; 0.099)	-0.220 (-0.438; -0.001)*
Model 2	0.003 (-0.035; 0.040)	-0.007 (-0.035; 0.020)	0.028 (-0.041; 0.098)	-0.219 (-0.437; -0.001)*
Model 3	0.003 (-0.035; 0.040)	-0.010 (-0.037; 0.018)	0.032 (-0.038; 0.102)	-0.207 (-0.427; 0.012)

Note. B, beta; CI, confidence interval; MBI, mild behavioral impairment.

Model 1: baseline age, gender/sex, practice effect

Model 2: baseline age, gender/sex, practice effect, employment status, ethnic origin, co-habitation status, education level

Model 3: baseline age, gender/sex, practice effect, employment status, ethnic origin, co-habitation status, education level, body-mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

*** $p<0.001$ ** $p<0.01$ * $p<0.05$

Supplementary Table S5 Association of MBI with the rate of decline in verbal reasoning in cognitively healthy analytical sample, stratified by gender/sex

	B (95% CI)	
	Verbal reasoning	
	Females	**Males**
MBI syndrome		
Model 1	-0.300 (-0.586; -0.014) *	-0.292 (-0.560; -0.023)*
Model 2	-0.301 (-0.586; -0.016) *	-0.292 (-0.560; -0.024)*
Model 3	-0.299 (-0.585; -0.013) *	-0.290 (-0.559; -0.022)*
Emotional dysregulation		
Model 1	-0.177 (-0.301; -0.053)**	-0.165 (-0.366; 0.037)
Model 2	-0.177 (-0.301; -0.053)**	-0.164 (-0.364; 0.037)
Model 3	-0.174 (-0.298; -0.049)**	-0.164 (-0.366; 0.038)
Decreased motivation		
Model 1	-0.234 (-0.377; -0.091)**	-0.307 (-0.517; -0.097)**
Model 2	-0.235 (-0.378; -0.092)**	-0.307 (-0.516; -0.098)**
Model 3	-0.226 (-0.370; -0.083)**	-0.308 (-0.518; -0.098)**
Impulse dyscontrol		
Model 1	-0.138 (-0.265; -0.011)*	-0.182 (-0.375; 0.012)
Model 2	-0.138 (-0.264; -0.011)*	-0.181 (-0.375; 0.012)
Model 3	-0.136 (-0.263; -0.009)*	-0.176 (-0.371; 0.018)
Social inappropriateness		
Model 1	-0.220 (-0.413; -0.028)*	-0.282 (-0.552; -0.012)*
Model 2	-0.222 (-0.414; -0.029)*	-0.281 (-0.551; -0.012)*
Model 3	-0.219 (-0.412; -0.026)*	-0.266 (-0.537; 0.005)
Psychotic symptoms		
Model 1	-0.175 (-0.427; 0.076)	-0.448 (-0.882; -0.015)*
Model 2	-0.174 (-0.425; 0.078)	-0.452 (-0.884; -0.019)*
Model 3	-0.157 (-0.410; 0.096)	-0.449 (-0.882; -0.016)*

Note. CI, confidence interval; MBI, mild behavioral impairment.

Model 1: baseline age, practice effect

Model 2: baseline age, practice effect, employment status, ethnic origin, co-habitation status, education level

Model 3: baseline age, practice effect, employment status, ethnic origin, co-habitation status, education level, body-mass index, hypertension, history of heart disease, diabetes, hypercholesterolemia

*** $p<0.001$ ** $p<0.01$ * $p<0.05$