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Original Article

Improving dementia prognostication in cognitively normal older adults: conventional versus novel approaches to modelling risk associated with neuropsychiatric symptoms

Maryam Ghahremani, Eric E. Smith and Zahinoor Ismail

Background

Studies in cognitively normal individuals on associations between psychiatric symptomatology and incident dementia have not reliably differentiated psychiatric syndromes from neuropsychiatric symptoms (NPS) that represent neurodegeneration. Conventional modelling often overlooks symptom natural history. Mild behavioural impairment (MBI) is a syndrome that leverages later-life emergent and persistent NPS to identify a high-risk group for incident dementia.

Aim

We aimed to explore associations of MBI, and conventionally-measured NPS (NPS-not-MBI), with incident dementia in cognitively normal individuals and the cognitively normal subset with subjective cognitive decline (SCD).

Method

Using National Alzheimer's Coordinating Center data, MBI was operationalised by the absence of past psychiatric disorders (symptom emergence) and the presence of symptoms at >2/3 of pre-dementia visits (symptom persistence). Kaplan–Meier survival curves and Cox proportional hazards regressions modelled dementia incidence across NPS groups and MBI domains, adjusted for age, gender, education, race, APOE-ε4, and cognitive status.

Results

The sample comprised 1408 MBI (age 75.2 ± 9.5; 54.3% female), 5625 NPS-not-MBI (age 71.6 ± 8.8; 65.5% female) and 5078 No-NPS (age 71.2 ± 8.9; 67.6% female) participants. Compared with No-NPS, MBI participants had lower dementia-free survival ($P < 0.0001$) and 2.76-fold greater adjusted dementia incidence rate (95% CI: 2.27–3.35, $P < 0.001$); incidence rate in NPS-not-MBI did not differ from No-NPS (hazard ratio 0.97, 95% CI: 0.82–1.14, $P = 0.687$). Of those with MBI who progressed to dementia, 76.0% developed Alzheimer's disease. Similarly, in the SCD subsample ($n = 3485$), persons with MBI had 1.99-fold greater dementia incidence versus No-NPS (95% CI: 1.46–2.71, $P < 0.001$) while NPS-not-MBI did not differ from No-NPS (hazard ratio 0.92, 95% CI: 0.70–1.19, $P = 0.511$).

Conclusions

Incorporating natural history into assessment of psychiatric symptoms in accordance with MBI criteria enhances dementia prognostication and modelling.

Keywords

Neuropsychiatric symptoms; mild behavioural impairment; normal cognition; subjective cognitive decline; incident dementia.

Neuropsychiatric symptoms (NPS) are psychiatric and behavioural aspects of dementia prevalent in ~97% of persons with Alzheimer's disease dementia.[1] NPS are consistently associated with greater dementia risk in individuals with mild cognitive impairment (MCI).[2,3] However, longitudinal studies have demonstrated that in 30% of Alzheimer's disease cases NPS can occur in advance of cognitive decline.[4,5] Therefore, appropriate characterisation of this behavioural prodrome may assist with earlier identification of dementia, especially among cognitively normal individuals with no objective cognitive changes to signal risk. Longitudinal studies in cognitively normal individuals have reported a greater incidence of dementia in individuals with NPS.[6–8] However, these studies captured NPS using a single-timepoint assessment, without considering symptom natural history. Thus, some of the identified NPS may have been related to long-standing psychiatric disorders rather than an emerging neurodegenerative disease. Furthermore, short reference frames of one to 4 weeks in conventional NPS questionnaires make it difficult to distinguish between persistent and transient NPS. Persistent NPS are more likely to represent behavioural manifestations of a progressive neurodegenerative disease, while transient NPS may arise from life stressors, potentially resolving if the stressor is removed. Mild behavioural impairment (MBI) is a validated syndrome, the criteria for which were developed to address these shortcomings in conventional approaches to NPS assessment. MBI leverages risk attendant with later-life emergent (age ≥50 years) and persistent (≥6 months) NPS to identify high-risk individuals for incident dementia.[9] Five core domains of MBI include affective dysregulation, decreased drive/motivation, impulse dyscontrol, social inappropriateness, and psychosis.[9] MBI can emerge at any point along the cognitive spectrum, from cognitively normal to subjective cognitive decline (SCD) – a self-perceived decline in cognitive ability without objective findings[10] through to MCI. Ultimately, change from longstanding patterns is one of the two cardinal MBI criteria (along with symptom persistence). A new presentation in someone with a history of a different psychiatric condition is of concern, potentially representing neuropsychiatric manifestations of early-stage neurodegenerative disease, consistent with MBI.[11] Several studies showed that MBI in cognitively normal individuals is associated with cognitive impairment and/or progression to MCI[5,12–17]; however, studies on the association of MBI and its domains with incident dementia are limited. Here, we explored associations of both MBI and conventionally measured NPS with incident dementia in cognitively normal older adults, including a subset with SCD. Further, we explored the association of each MBI domain with incident dementia across the whole sample. We hypothesised greater dementia

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incidence in MBI, compared with conventionally measured NPS not meeting MBI criteria (NPS-not-MBI) and No-NPS, and greater dementia incidence for every MBI domain.

Method

Study population

Data were obtained from the National Alzheimer's Coordinating Centre (https://naccdata.org), with a March 2022 data freeze. NACC was established by the National Institute on Aging (NIA) and consists of multiple NIA-funded Alzheimer's Disease Research Centers (ADRCs) recruiting and collecting data from individuals with cognitive function ranging from normal cognition to dementia. The NACC Uniform Data Set (UDS) is a large prospective and longitudinal clinical evaluation that includes demographic and standardised clinical data collected approximately annually. All contributing ADRCs were required to administer standardised forms, obtain informed consent from participants and their informants, and institutional review board approvals prior to submitting data to NACC. Detailed information on the cohort are described elsewhere.[18–20]

Participant selection

To satisfy the MBI criterion of later-life symptom emergence, only participants with no reported history of psychiatric or neurodevelopmental disorders were included. Participants required complete Neuropsychiatric Inventory Questionnaire (NPI-Q) data to determine MBI status. MBI domain scores were derived from NPI-Q domain scores using a published algorithm.[21,22] MBI total score was the sum of domain scores, representing global MBI. The MBI symptom persistence criterion was operationalised using a validated approach requiring NPS presence (MBI score >0) at more than two-thirds of all study visits prior to dementia diagnosis.[23] The comparator group comprised participants with no NPS prior to dementia onset, irrespective of psychiatric history (No-NPS). A second comparator group (NPS-not-MBI) comprised participants not meeting the MBI later-life symptom emergence and persistence criteria. In all NPS groups, the NACC clinical cognitive diagnosis was used to ensure only cognitively normal participants at baseline were included, based on a global clinical dementia rating scale (CDR Dementia Staging Instrument) score of 0 and/or neuropsychological testing within normal range. As a sensitivity analysis, a cognitively normal subsample was generated including only those with SCD. SCD was determined by participant endorsement of memory decline on the NACC UDS B9 form and absent objective cognitive changes, as per the SCD-initiative workgroup criteria.[10] Participants with no follow-up visits and those missing values on covariates of interest were excluded; their NPS profile did not differ from those with complete data.

Statistical analysis

Baseline demographic, clinical, and genetic variables considered in the analyses included age, gender, education years, race, and APOE-ε4 status. For the primary cognitively normal sample analysis, SCD status was included in the model. Race was categorised as White, Black, or Other. The Other race group included Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islanders or other races as specified in the UDS, merged into one category due to the small sample size per race. APOE-ε4 status was categorised as carrier and noncarrier, with carriers having one or two copies of the ε4 allele and noncarriers having none. Each variable was compared across NPS groups to identify significant baseline differences, using *t*-tests for continuous variables and χ^2 tests for categorical variables.

Kaplan–Meier survival curves compared 10-year dementia-free survival across NPS groups, with log-rank test assessing between-group differences. Cox proportional hazards models assessed hazard ratios for dementia over 10 years, adjusted for age, gender, education, race, APOE-ε4 status and SCD status. Hazard ratios were accompanied by their associated 95% confidence interval (CI) and *P*-value.

Interaction terms between NPS groups and gender, race, APOE-ε4 status and SCD status were included to explore effect modification across strata of each covariate. The dementia incidence rate for MBI was assessed within strata of each covariate and compared with No-NPS and NPS-not-MBI groups. Multiplicative interaction tests assessed between-strata differences in the observed estimates.

A similar analysis was implemented to explore the association of NPS groups with incident dementia in the subsample of cognitively normal participants with SCD at baseline, adjusting for age, gender, education, race and APOE-ε4 status.

Secondary analyses were performed to distinguish individual associations of each MBI domain with incident dementia across the whole sample, by implementing adjusted Cox models for each MBI domain.

All statistical analyses were performed in RStudio v1.3.1093, using the *survival* package for Cox proportional hazards models, and *ggplot2* and *survminer* for Kaplan–Meier curves and forest plots. Assumptions for proportional hazards were assessed using the *cox.zph* function from the *survival* package.

Results

Dementia incidence rate across NPS groups in cognitively normal older adults

Details of the participant selection process leading to the final study sample of 12 111 participants are illustrated in Supplementary Fig. 1 available at https://doi.org/10.1192/bjp.2024.136. The cognitively normal sample comprised 5078 participants with no NPS prior to dementia diagnosis (mean age 71.2 ± 8.9; 67.6% female), 5625 with NPS-not-MBI (mean age 71.6 ± 8.8; 65.5% female) and 1408 with MBI (mean age 75.2 ± 9.5; 54.3% female). Both NPS-not-MBI and MBI groups differed significantly from the No-NPS group in terms of age (NPS-not-MBI: $P = 0.011$; MBI: $P < 0.001$), gender (NPS-not-MBI: $P = 0.018$; MBI: $P < 0.001$), education (NPS-not-MBI: $P = 0.027$; MBI: $P < 0.001$), race ($P < 0.001$) and SCD status ($P < 0.001$). The No-NPS group was younger and more educated, with fewer White participants and more women. SCD was more prevalent in both NPS-not-MBI and MBI, compared with No-NPS. No significant differences were found for APOE-ε4 status (Supplementary Table 1).

The average follow-up time was 4.45 years for the No-NPS group, 5.74 years for NPS-not-MBI and 3.73 years for MBI. Compared with the No-NPS group, 10-year dementia-free survival was lower in MBI ($P < 0.0001$), while not significantly different for NPS-not-MBI (Fig. 1(a)). The 5-year survival probability was 95.7% (CI: 95.0–96.4%) for No-NPS, 95.7% (CI: 95.1–96.4%) for NPS-not-MBI and 81.5% (CI: 78.7–84.4%) for MBI. Compared with No-NPS, MBI had a 2.76-fold greater adjusted dementia incidence rate (CI: 2.27–3.35, $P < 0.001$), while NPS-not-MBI did not differ (adjusted hazard ratio 0.97, CI: 0.82–1.14, $P = 0.687$). SCD at baseline was associated with a 2.11-fold greater adjusted dementia incidence rate than SCD– (CI: 1.83–2.43, $P < 0.001$) (Table 1), with a 5-year survival probability of 90.7% (89.6–91.9%) for SCD+ versus 95.8% (95.3–96.3%) for SCD–. No significant interaction of NPS group was found with gender, race or APOE-ε4 status. However, the association between NPS status and incident dementia differed between the strata of SCD–, such that the relative impact of MBI was lower

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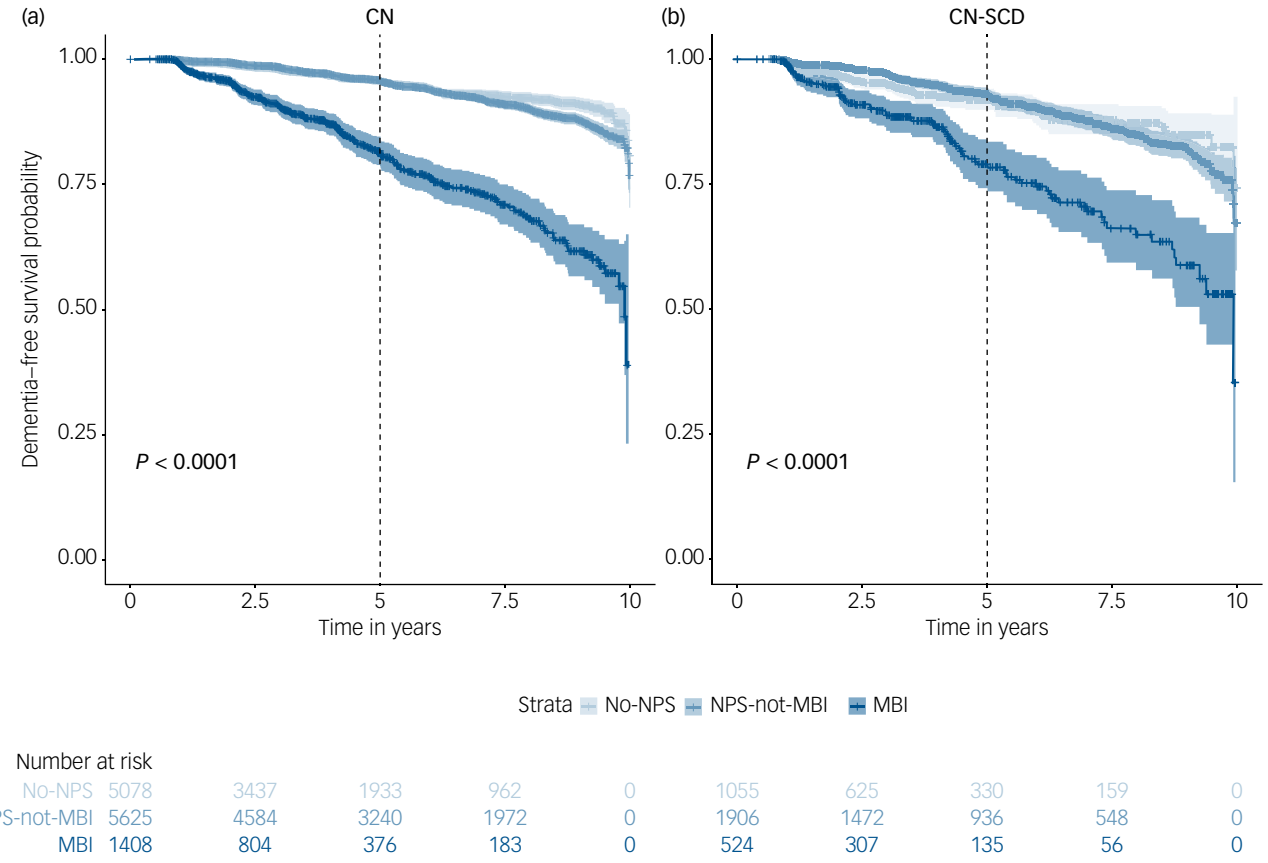

Fig. 1 Kaplan–Meier curves of 10-year dementia-free survival stratified by neuropsychiatric symptoms (NPS) groups (No-NPS versus NPS-not-MBI versus MBI) for (a) cognitively normal (CN) individuals and (b) those with subjective cognitive decline (SCD) at baseline. The vertical dashed line marks the 5-year dementia-free survival.

within the SCD+ group (hazard ratio 1.96, CI: 1.44–2.66, $P < 0.001$) than in the SCD– group (hazard ratio 3.53, CI: 2.77–4.51, $P < 0.001$), while no significant differences were found for NPS-not-MBI (SCD–: hazard ratio 0.99, CI: 0.80–1.23, $P = 0.911$; SCD+: hazard ratio 0.88, CI: 0.68–1.15, $P = 0.365$) (multiplicative interaction test: MBI SCD+ versus MBI SCD–: hazard ratio 0.56, CI: 0.38–0.82, $P = 0.003$; NPS-not-MBI SCD+ *v.* NPS-not-MBI SCD–: hazard ratio 0.89, CI: 0.64–1.26, $P = 0.530$). For MBI, the hazard ratio for dementia was 5.10 (CI: 3.90–6.66; $P < 0.001$) in the SCD + group and 3.53 (CI: 2.77–4.51, $P < 0.001$) in SCD–. For NPS-not-MBI, the hazard ratio for dementia was 2.30 (CI: 1.85–2.86; $P < 0.001$) in the SCD+ group and 0.99 (CI: 0.80–1.23, $P = 0.911$) in SCD–. For No-NPS, the hazard ratio for dementia was 2.60 (CI: 1.97–3.44, $P < 0.001$) for SCD+ compared with hazard ratio 1 (reference) for SCD– (Supplementary Table 3).

In total, 837 cognitively normal participants (6.91%) progressed to dementia over 10 years. Of the 1408 participants with MBI, 217 (15.4%) progressed to dementia, comprising 165 (76.0%) with

Table 1 Hazard ratio for incident dementia, associated with each variable in the Cox proportional hazards models for cognitively normal individuals and a subset of those with subjective cognitive decline at baseline

Cognitive status		CN ($n = 12\,111$)		SCD ($n = 3485$)	
Variable	Subgroup	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
NPS group	No-NPS	Reference		Reference	
	NPS-not-MBI	0.97 [0.82, 1.14]	0.687	0.92 [0.70, 1.19]	0.511
	MBI	2.76 [2.27, 3.35]	**<0.001**	1.99 [1.46, 2.71]	**<0.001**
Age	–	1.10 [1.10, 1.12]	**<0.001**	1.09 [1.08, 1.11]	**<0.001**
Gender	Male	Reference	0.866	Reference	0.597
	Female	0.99 [0.86, 1.14]		1.06 [0.85, 1.32]	
Education	–	0.94 [0.92, 0.96]	**<0.001**	0.94 [0.91, 0.97]	**<0.001**
Race	White	Reference		Reference	
	Black	0.76 [0.60, 0.95]	**0.015**	0.80 [0.58, 1.11]	0.179
	Other	0.81 [0.52, 1.29]	0.377	1.08 [0.64, 1.83]	0.768
APOE-ε4	Noncarrier	Reference	**<0.001**	Reference	**<0.001**
	Carrier	2.32 [2.01, 2.65]		2.34 [1.90, 2.89]	
SCD	Absent	Reference	**<0.001**		
	Present	2.11 [1.83, 2.43]			

CN, cognitively normal; SCD, subjective cognitive decline; HR, hazard ratio; NPS, neuropsychiatric symptoms; MBI, mild behavioural impairment. Bold *P*-values indicate statistical significance ($P < 0.05$).

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Alzheimer's disease, eight (3.7%) with behavioural variant frontotemporal dementia (bvFTD), two (0.9%) with Lewy Body dementia (LBD), three (1.4%) with vascular dementia (VaD), and 39 (18.0%) with unrecorded dementia subtypes. Among the 5625 participants with NPS-not-MBI, 404 (7.2%) progressed to dementia, consisting of 326 (80.7%) with Alzheimer's disease, seven (1.7%) with bvFTD, eight (2.0%) with LBD, 16 (4.0%) with VaD and 47 (11.6%) with unrecorded dementia subtypes. Finally, among the 5078 No-NPS participants, 216 (4.3%) progressed to dementia, consisting of 183 (84.7%) with Alzheimer's disease, one (0.5%) with bvFTD, four (1.9%) with LBD, five (2.3%) with VaD and 23 (10.6%) with unrecorded dementia subtypes (Fig. 2).

Dementia incidence rate across NPS groups in cognitively normal older adults with SCD

The SCD sample comprised 1055 participants in the No-NPS group (mean age 71.2 ± 8.9; 68.5% female), 1906 in NPS-not-MBI (mean age 71.1 ± 8.7; 64.7% female) and 524 in MBI (mean age 74.5 ± 9.2; 53.1% female). Compared with No-NPS, the MBI group was older ($P < 0.001$), less educated ($P = 0.006$) and had fewer female ($P < 0.001$) and White ($P = 0.003$) participants; the NPS-not-MBI group was less educated ($P = 0.039$) and had more female ($P = 0.041$) and White ($P = 0.002$) participants (Supplementary Table 2).

Compared with No-NPS, 10-year dementia-free survival was lower for MBI ($P < 0.0001$) but not for NPS-not-MBI (Fig. 1(b)). The 5-year survival probability was 91.9% (CI: 89.9–94.0%) for No-NPS, 92.8% (CI: 91.5–94.2%) for NPS-not-MBI, and 79.0% (CI: 74.3–84.0%) for MBI. Compared with No-NPS, MBI had a 1.99-fold greater adjusted dementia incidence rate (CI: 1.46–2.71, $P < 0.001$), while NPS-not-MBI did not differ (adjusted hazard ratio 0.92, CI: 0.70–1.19, $P = 0.511$) (Table 1). No significant interaction of NPS group was found with gender, race or APOE-ε4 status.

In total, 361 participants with SCD progressed to dementia over 10 years. Within the MBI group, 17.2% progressed to dementia, comprising 86.7% Alzheimer's disease, 3.3% bvFTD, 1.1% LBD and 8.9% unrecorded dementia subtypes. Within the NPS-not-MBI group, 10.3% progressed to dementia, consisting of 81.4% Alzheimer's disease, 2.6% bvFTD, 2.1% LBD, 4.1% VaD and 9.8% unrecorded dementia subtypes. Within the No-NPS group, 7.3% progressed to dementia, consisting of 84.4% Alzheimer's disease, 1.3% bvFTD, 3.9% LBD, 2.6% VaD and 7.8% unrecorded dementia subtypes (Fig. 2).

Individual association of MBI domains with incident dementia in cognitively normal older adults

The sample comprised 738 participants with MBI-affective dysregulation, 165 with MBI-decreased motivation, 710 with MBI-impulse dyscontrol, 79 with MBI-social inappropriateness and 26 with MBI-psychosis. Compared with No-NPS, dementia-free survival was lower across all MBI domains ($P < 0.0001$). The adjusted hazard ratios in decreasing order were MBI-psychosis (15.80, CI: 8.43–29.63, $P < 0.001$), MBI-social inappropriateness (7.86, CI: 5.33–11.60, $P < 0.001$), MBI-apathy (6.47, CI: 4.66–8.97, $P < 0.001$), MBI-impulse dyscontrol (3.08, CI: 2.42–3.93, $P < 0.001$) and MBI-affective dysregulation (2.93, CI: 2.31–3.72, $P < 0.001$) (Table 2).

Discussion

In this longitudinal study of 12 111 cognitively normal participants, individuals with MBI had a 2.76-fold greater dementia incidence rate than those with no NPS, a difference not seen for those with NPS not meeting MBI criteria. Similar findings were observed in the subgroup of individuals with SCD. All MBI domains were associated with greater dementia incidence rate than no NPS, with MBI-psychosis having the highest hazard ratio and MBI-affective symptoms the lowest. The majority of dementia progressors with MBI progressed to Alzheimer's disease. These findings emphasise the importance of the core MBI criteria of symptom emergence and persistence in operationalising NPS-related dementia risk.

Several studies have reported on the association of global MBI with cognitive impairment and incident dementia. In a cross-sectional study of 499 participants with NPS assessed using the MBI-checklist (MBI-C),[24] the MBI group demonstrated poorer performance in memory and executive function compared with no-MBI.[12] A recent study that operationalised MBI using a single-timepoint NPS measure reported that MBI in cognitively normal participants was a significant predictor of progression to clinically diagnosed (hazard ratio 1.75) and neuropathologically confirmed Alzheimer's disease (hazard ratio 1.59).[25] In a longitudinal study of 9931 older adults without MCI or dementia, participants with MBI (captured with MBI-C) had a significantly worse baseline cognitive performance and greater decline in attention and working memory.[13] An extension of this cohort with 8181 dementia-free older adults reported both cross-sectional and longitudinal associations between MBI and cognitive performance, with a moderating effect of gender. MBI and all its domains

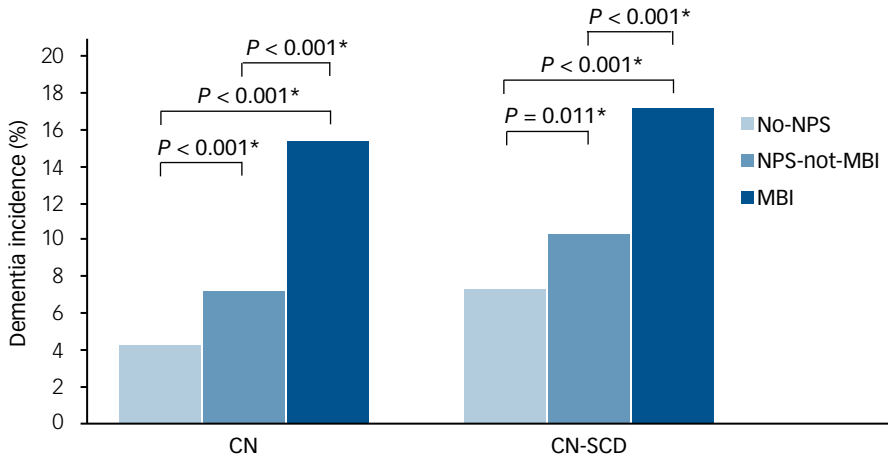

Fig. 2 Ten-year dementia incidence across neuropsychiatric symptoms (NPS) groups (No-NPS versus NPS-not-MBI versus MBI) for cognitively normal (CN) individuals and those with subjective cognitive decline (SCD) at baseline.

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Table 2 Hazard ratios for incident dementia for the five domains of mild behavioural impairment compared with No-NPS in the total sample of cognitively normal older adults at baseline

MBI domain	*N*	HR [95% CI]	*P*-value
MBI-psychosis	26	15.80 [8.43, 29.63]	**<0.001**
MBI-social inappropriateness	79	7.86 [5.33, 11.60]	**<0.001**
MBI-decreased motivation	165	6.47 [4.66, 8.97]	**<0.001**
MBI-impulse dyscontrol	710	3.08 [2.42, 3.93]	**<0.001**
MBI-affective dysregulation	738	2.93 [2.31, 3.72]	**<0.001**

NPS, neuropsychiatric symptoms; HR, hazard ratio; MBI, mild behavioural impairment. Bold *P*-values indicate statistical significance ($P < 0.05$).

were significantly associated with cognitive decline, with a higher rate of decline in men than women.[26] In our sample of 12 111 cognitively normal older adults, participants with MBI had a 2.76-fold greater dementia incidence rate than those with no NPS prior to dementia onset. In contrast, no significant difference in dementia incidence rate was found for participants with NPS not meeting MBI criteria (NPS-not-MBI). While no moderating effect of gender was identified in our study, our findings are in line with the previous literature on the association of NPS with a greater rate of incident cognitive decline and dementia in cognitively unimpaired older adults.

Previous studies have also explored the association between NPS domains and incident dementia in cognitively normal older adults. A 14-year study of 4922 older men demonstrated that participants with depression (captured by the Geriatric Depression Scale), especially at the start of the follow-up period, were at greater dementia risk that those without.[6] A NACC study of 4517 participants explored the risk of progression to MCI or dementia across four classes of NPI-Q-assessed NPS. The greatest risk was reported for the multiple NPS class, followed by depressed and irritable classes. While each NPI-Q domain except elation was associated with a significantly greater risk of progression to MCI or dementia, delusions and hallucinations had the highest hazard ratio (4.5 and 3.4, respectively) despite relatively rare endorsement.[27] Another study of 12 452 participants reported an association between baseline NPI-Q-measured psychosis (hazard ratio 3.6), agitation (hazard ratio 1.6) and affective symptoms (hazard ratio 1.5) and greater dementia risk, with psychosis having the greatest risk.[8] Our MBI domain-level analyses revealed similar findings, with a 15.80-fold greater dementia incidence rate for MBI-psychosis, a 3.08-fold greater rate for MBI-impulse dyscontrol (encompassing agitation), and a 2.93-fold greater rate for MBI-affective dysregulation (encompassing depression).

With regard to MBI domain-level findings in cognitively normal participants, one NACC study using a single-timepoint NPS measure to operationalise MBI reported that all MBI domains were associated with Alzheimer's disease, with psychosis having the greatest effect (hazard ratio 6.49).[25] Other NACC studies also reported on specific MBI domains in mixed samples of cognitively normal individuals and those with MCI, with MBI-domain status determined based on symptom presence across two consecutive visits to meet the MBI symptom persistence criterion. In these studies, compared with No-NPS, the hazard ratio for dementia was 3.76 for MBI-psychosis,[28] 2.69 for MBI-apathy[29] and 1.76 for MBI-affective dysregulation.[30] In our MBI domain analyses, all domains were associated with greater dementia incidence; however, the hazard ratios were substantially higher than those of the previous literature, likely due to the methodological differences in capturing NPS. Our study operationalised the MBI symptom persistence criterion by capturing the presence of NPS across at least two-thirds of pre-dementia visits. In the three NACC studies on MBI psychosis, apathy, and affective dysregulation domains, the symptom persistence criterion was operationalised using two consecutive visits.[28–30] Moreover, in these studies, all participants with a history of psychiatric disorders were excluded prior to assigning NPS group, thus primarily assessing the utility of the *symptom persistence criterion*. In our study, the exclusion criterion for history of psychiatric conditions was only applied to participants in the MBI group, better operationalising both core MBI criteria, identifying NPS that were more likely to represent sequelae of neurodegenerative disease, potentially at a preclinical or precognitive stage. Further, these domain-level studies evaluated mixed dementia-free samples of cognitively normal individuals and MCI, with interaction terms to determine cognitive status-specific hazard ratios. In the cognitively normal MBI-psychosis group, for example, the hazard ratio was 9.96 versus no-NPS, compared with 3.38 in MCI MBI-psychosis.[28] Similarly, for MBI-apathy, the hazard ratio in cognitively normal individuals was 5.91 versus 2.16 in MCI[29] and for MBI-affective dysregulation, the hazard ratio in cognitively normal individuals was 2.59 versus 1.50 in MCI.[30]

To our knowledge, the only study on the association of MBI-impulse dyscontrol and MBI-social inappropriateness with incident dementia reported adjusted hazard ratios of 2.02 and 2.25 for each domain, respectively, using a single-timepoint NPS assessment.[25] The present study used a more precise approach to operationalise both MBI core criteria of symptom emergence and persistence and demonstrated significant associations of these domains with incident dementia in cognitively normal older adults, but with a greater magnitude of effect (hazard ratio 7.86 for MBI-social inappropriateness, hazard ratio 3.08 for MBI-impulse dyscontrol). While social inappropriateness and its association with incident dementia is understudied, previous literature indicate deficits in social cognition in MCI[31–34] and dementia.[35,36] Our study demonstrates that even in a state of objectively normal cognition, older adults can present with socially inappropriate behaviours that may be the first sign of an unrecognised neurodegenerative disease in advance of noticeable cognitive impairments. Similarly, symptoms of impulsivity and agitation are common in MCI.[37–39] In a cross-sectional study of 1377 dementia-free older adults, MBI-impulse dyscontrol was among the most prevalent domains, with frequencies of 17.2% in normal cognition, 28.7% in SCD and 33.8% in MCI, although assessed using a single-timepoint NPS measure.[40] Unfortunately, patients expressing socially inappropriate or impulsive behaviours are often misdiagnosed with a psychiatric disorder, without recognising that symptoms may represent early manifestations of an underlying neurodegenerative disease.[41,42] Our findings demonstrate that in cognitively normal older adults, later-life emergent and persistent socially inappropriate and impulsive behaviours are significantly associated with greater dementia incidence rates. Earlier identification of these symptoms could identify treatment targets, potentially improving quality of life for patients and their caregivers.

In our analyses, for both the cognitively normal sample and the SCD subsample, across NPS groups, MBI had the highest percentage of participants progressing to dementia (Fig. 2). Among progressors across all NPS groups, the majority progressed to Alzheimer's disease dementia and only few had bvFTD, LBD or VaD, a result which may be surprising to some. However, given the high population prevalence of Alzheimer's disease relative to other dementias, the fact that 30% of Alzheimer's disease cases have a behavioural prodrome, and that defining the risk group in accordance with MBI criteria provides more specificity, this result is rather expected.

Despite fewer studies on NPS and SCD compared with MCI, evidence suggests an association between NPS and incident dementia in older adults with SCD. In a longitudinal study of 579 710 older

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adults, while SCD was significantly associated with greater dementia risk, the risk was greater still in the presence of depressive symptoms.[43] Similar findings were reported in a longitudinal study of 2415 cognitively unimpaired older adults, in which the risk of dementia roughly doubled in participants with SCD and worry symptoms compared with SCD alone.[44] Furthermore, in a NACC study of 2769 cognitively unimpaired (CDR = 0) older adults, the combination of MBI and SCD was associated with a greater likelihood of CDR progression to ≥0.5 at 3 years compared with either MBI or SCD alone.[5]

In our primary analysis of 12 111 cognitively normal participants, compared with the reference group with no SCD and no NPS, the co-occurrence of MBI and SCD had the highest hazard ratio for incident dementia (hazard ratio 5.10, CI: 3.90–6.66) compared with when SCD was present with no NPS (hazard ratio 2.60, CI: 1.97–3.44) or with NPS-not-MBI (hazard ratio 2.30, CI: 1.85–2.86) (Supplementary Table 3). These findings are consistent with the previous 3-year study of CDR progression.[5] In our interaction analysis, the relative impact of MBI on dementia risk within the SCD stratum was lower (hazard ratio 1.96) than the impact of MBI in the cognitively normal stratum (hazard ratio 3.53). This is while the relative impact of NPS-not-MBI was 0.88 in SCD and 0.99 in cognitively normal individuals, indicating that NPS-not-MBI are not significant contributors to dementia risk over no NPS. These findings are consistent with several previous analyses in mixed dementia-free samples, with the same intuitive explanation for the interaction across cognitive strata.[28–30,45] In cognitively unimpaired participants without subjective memory complaints, cognitive status contributes little to risk, which is driven by behavioural status (namely MBI, as NPS-not-MBI did not differ from No-NPS). However, subjective memory complaints may indicate a more advanced disease stage than normal cognition. Correspondingly, the relative impact of behaviour on risk is less in SCD versus normal cognition, as cognitive symptoms also contribute to risk. Importantly, the absolute risk is greater in this group (hazard ratio 5.10 in SCD versus hazard ratio 3.53 in cognitively normal individuals), which represents an interaction of cognitive risk and behavioural risk.

The sensitivity analysis was also informative. In the SCD sample of 3485 participants, MBI had a greater hazard ratio for incident dementia (hazard ratio 1.99) than NPS-not-MBI (hazard ratio 0.92) and No-NPS (reference level; hazard ratio 1). These findings provide additional evidence that different approaches to incorporating NPS into dementia prognostication can result in significantly different estimates. The incorporation of natural history (symptom emergence in later-life and symptom persistence) into the predictor representing behavioural symptoms improves the prognostic power of these behavioural symptoms over what has traditionally been a cross sectional measure. Thus, adding MBI status to the traditional assessment of risk represented by cognitive status could improve the specificity of the risk estimate.

Limitations

Despite the strength of our findings, this study is not without limitations. NACC constitutes mostly highly educated white participants and is not fully representative of the community population. One can speculate that Black and other racialised NACC participants are more removed from the general population of racialised persons, selecting a subset who live closer to academic centres, are more trusting of the medical system, and who are better able to attend study visits during office hours in lieu of work. Future iterations of the NACC UDS will improve sample representativeness, hopefully reducing this potential bias. In our study, MBI was operationalised based on NPI-Q, which necessitated the exclusion of participants with prior psychiatric conditions to account for the MBI criterion of de novo symptom emergence in later-life representing a change from longstanding patterns. Furthermore, while the two-thirds of all study visits approach fulfilled the MBI symptom persistence criterion, it is unclear whether symptoms were present between study visits due to the one-month reference range of NPI-Q. Additionally, as the NPI-Q has not been validated in cognitively normal individuals, it may not be sensitive to all behavioural changes in this population. The use of validated NPS assessment scales such as the MBI-C that are specifically designed to capture MBI could mitigate these limitations. The MBI-C explicitly captures later-life emergent and persistent NPS and has a 6-month reference frame, allowing the MBI status to be determined at a single visit.[24,46,47] The MBI-C has recently been included in NACC and can be incorporated in the future. Finally, this study design does not determine causality. Questions still remain as to whether cognitive and behavioural risk represent different aetiologies, or different phenotypes of a common aetiology. Most MBI progressors in this study developed Alzheimer's disease. Several studies across the cognitive continuum have linked MBI with Alzheimer's disease proteinopathies over No-NPS, No-MBI and NPS-not-MBI.[45,48] However, additional research is required, as this study simply provided risk estimates based on behavioural status modified by cognitive status.

Overall, our findings add to the evidence base that later-life symptom emergence and persistence, the cardinal criteria of MBI, can be used to prognosticate dementia better than conventional approaches of incorporating NPS into modelling. The natural history of symptoms is an important aspect of dementia assessment, especially in older adults without objective cognitive impairment. Further, while all MBI domains were associated with greater dementia risk, psychosis had the greatest contribution to risk and affective symptoms the lowest, despite depression often being the NPS used in most prognostic models. Globally, assessment for MBI provides a cost-effective and scalable tool for early detection of risk in cognitively normal older adults, even more so when objective cognitive impairment is absent to signal risk.

Maryam Ghahremani, Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, Canada; Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada; **Eric E. Smith**, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada; Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, Canada; Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada; **Zahinoor Ismail**, Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, Canada; Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada; Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, Canada; Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada; O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, Canada; and Clinical and Biomedical Sciences, Faculty of Health and Life Sciences, University of Exeter, Exeter, UK

Correspondence: Zahinoor Ismail. Email: ismailz@ucalgary.ca

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Supplementary material

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Data availability

All data used in preparing this manuscript are publicly available on request from the NACC Data Request platform (https://nacc.redcap.rit.uw.edu/surveys/?s=KHNPKLJW8TKAD4DA).

Analytic code availability

All analyses included in this manuscript were conducted using standard publicly available R packages in RStudio. Custom codes that support the findings of this study are available from the corresponding author on request.

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Author contributions

All authors made substantial contributions to the analysis, interpretation of data and preparation of the manuscript. M.G. contributed to the study design, conducted data cleaning and statistical analyses, drafted the initial manuscript and managed revisions to produce the final version. E.E.S. reviewed the statistical modeling and results and contributed to data interpretation and manuscript revision. Z.I. designed the study, reviewed the data and contributed to the analysis, interpretation and manuscript writing. All authors reviewed the final manuscript, had full access to the data and accept responsibility for submitting the manuscript for publication.

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Declaration of interest

Z.I. has served as a consultant/advisor for Eisai, Lilly, Lundbeck/Otsuka, Novo Nordisk and Roche. E.E.S. and M.G. declare that there is no conflict of interest.

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