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Mild Behavioral Impairment and Quality of Life in Community Dwelling Older Adults

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ABSTRACT

Objectives: Mild behavioral impairment (MBI) is a dementia risk indicator in older adults characterized by later-life emergent and persistent neuropsychiatric symptoms. Quality of life (QoL) is a multi-dimensional concept encompassing physical, spiritual, and emotional well-being. QoL aims to measure and quantify perceptions of individual health, well-being, standard of living, personal fulfillment, and satisfaction. As MBI symptoms may arise from early-stage neurodegenerative disease, MBI may contribute to declining QoL before dementia onset. In this study, we investigated the relationship between symptoms of MBI and QoL in older adults.

Methods: The sample comprised 1107 individuals aged ≥ 50 years from the Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behavior, Function, and Caregiving in Aging (CAN-PROTECT). Multivariable linear regressions were used to model the associations between MBI symptom severity (exposure), measured using the MBI Checklist (MBI-C), and QoL (outcome) assessed by the EuroQol-5D (EQ-5D, higher score = poorer QoL) and the novel Quality of Life and Function Five Domain Scale (QFS-5) (QFS-5, lower score = poorer QoL). Covariates were age, sex, cognition, education, ethnocultural origin, marital status, employment status, high blood pressure, heart disease, and diabetes. Moderation analysis explored potential sex differences. A sensitivity analysis was performed removing anxiety/depression items from the EQ-5D score.

Results: Across the sample (mean age = 64.4 ± 7.2, 79.4% female) every 1-point increase in MBI-C score was associated with a 0.06-point standard deviation (SD) increase in EQ-5D score (95% confidence interval (CI): 0.05–0.06, $p < 0.001$) and 0.08 SD decrease in QFS-5 score (95% CI: −0.09 to −0.08, $p < 0.001$). Neither association depended on sex ($p = 0.59$ and $p = 0.41$, respectively). The association remained significant after removing anxiety/depression items from the EQ-5D score ($\beta = 0.04$, 95% CI: 0.03– 0.04, $p < 0.001$).

Conclusions: The study shows that MBI is associated with poorer QoL, independent of sex, on two QoL scales. We addressed depression/anxiety items in the EQ-5D as a potential confounder for the observed MBI-QoL association by conducting a sensitivity analysis that excluded those items from the EQ-5D total score and by employing a novel measure of QoL (QFS-5) that excludes psychiatric symptoms from measurement of QoL. Associations of MBI with the novel QFS-5 were similar to associations between MBI and the EQ-5D. Finding interventions to reduce the burden of MBI symptoms might improve quality of life.

1 | Introduction

Globally, approximately 50 million people have dementia, and this number is expected to double every 20 years [1]. Dementia has a substantial impact on the global economy, estimated to be a 2 trillion-dollar disease by 2030 [1]. Additionally, there is a profound dementia-related burden on individuals, caregivers [2], and health systems [3].

Alzheimer disease (AD), the most common cause of dementia, contributes to the bulk of dementia-related burden [4]. However, AD begins decades before dementia diagnosis, first progressing through preclinical and prodromal disease stages [5]. Accordingly, the field has moved toward more robust assessment of risk factors, and earlier identification of disease. Mild cognitive impairment (MCI) has been established as an indicator of risk [6, 7], and subjective cognitive decline (SCD) [8] can identify risk even earlier in the disease course. Extending this work on cognition, measures of behavior and function have been explored as risk factors and leveraged as disease markers for early detection, with aims of administering preventative interventions and reducing overall burden [9–12].

An emerging approach to risk assessment is to incorporate neuropsychiatric symptoms (NPS) into prognostic models [13]. The diagnostic criteria for mild behavioral impairment (MBI) leverage NPS that are of later-life onset, and which persist, to identify persons at risk for cognitive decline and incident dementia [14–19]. MBI symptoms fall into five different domains: decreased drive and motivation (apathy), affective dysregulation (mood and anxiety symptoms), impulse dyscontrol (agitation, impulsivity, abnormal reward salience), social inappropriateness (impaired social cognition), and abnormal perception or thought content (psychosis) [14]. For some, MBI represents preclinical or prodromal disease [20–26]. An aim with the development of MBI criteria was to foster the addition of behavior to cognition to refine risk assessment, and to identify targets for earlier intervention to prevent disease and reduce dementia-related burden.

Health-related QoL is a broad multi-dimensional concept encompassing physical, social, and emotional factors of well-being linked to health-related stressors [27]. Assessment of QoL can provide insights into the impact of dementia on the patient [28], serving as a potential marker of dementia-related burden [29]. Indeed, QoL is impaired in persons with dementia [30]. However, in keeping with the notion of diseases that slowly accumulate and progress, disability and burden can start before syndromic dementia. Specifically, QoL impairment is evident during MCI [31] and SCD [32]. Therefore, it is important to measure QoL in at-risk persons and explore associations with disease markers, even in advance of overt health-related impairments. This line of research may identify factors contributing to poorer QoL, which may serve as additional targets to reduce burden.

Previously, in clinic outpatients, MBI has been associated with poorer QoL [33]. Here, we investigated the association between MBI and QoL in a sample of community dwelling, dementia-free older adults. We hypothesized more severe MBI symptoms would be associated with poorer QoL, measured by the EuroQol-5D (EQ-5D) and the Quality of Life and Function Five Domain Scale (QFS-5), the latter of which does not conflate depression/anxiety with QoL. Psychiatric disorders have well-known global disease burden and disability years [34], we anticipate that psychiatric symptomatology caused by neurodegenerative disease should also have measurable effects on QoL. We also explored potential sex differences, hypothesizing that MBI-QoL associations would be stronger in males than females, in keeping with MBI sex differences in cognition [35] and frailty [36, 37]. Sex differences were also critical to explore given potential sex-associated differences in QoL assessments across different settings [38, 39].

2 | Materials and Methods

2.1 | Setting

Data are from The Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behavior, Function, and Caregiving in Aging (CAN-PROTECT). Launched in March 2023, CAN-PROTECT is a nation-wide online longitudinal observational cohort study of brain aging; all Canadian residents aged ≥ 18 years without dementia diagnosis are eligible. CAN-PROTECT measures risk and resilience to brain aging, incorporating a validated neuropsychological test battery, detailed assessment of demographics, and a series of self- and informant-reported questionnaires. Administered annually, questionnaires assess cognition, behavior, function, health, wellness, lifestyle, medical and psychiatric history, and QoL. CAN-PROTECT received ethics approval from the Conjoint Health Research Ethics Board at the University of Calgary (REB21-1065). A more detailed description of CAN-PROTECT has been published previously [40].

2.2 | Participants

Of 1984 CAN-PROTECT study participants, inclusion criteria for this analysis were: (1) completion of the MBI-Checklist (MBI-C); (2) completion of the QoL questionnaires; and (3) age ≥ 50 years, as per the International Society to Advance Alzheimer's Research and Treatment (ISTAART) diagnostic

Summary

- In this sample of older Canadians without dementia, greater MBI symptom severity was associated with poorer QoL, independent of sex.
- These results suggest that emergent and persistent behavioral symptoms in dementia-free older adults may have widespread sequelae, reflected by poorer QoL.
- By utilizing both the novel Quality of Life and Function Five Domain Scale (QFS-5) and EQ-5D, we demonstrate that MBI is associated with poorer QoL.

criteria for MBI [14]. A final sample size of 1107 participants were included (see Figure 1 for flow diagram).

2.3 | Measures

From the demographics questionnaire, items relevant to this study included age, cognition, sex, years of education, ethnocultural origin, marital status, and employment status. Self-reported information about clinical diagnoses of heart disease, high blood pressure, and diabetes were also incorporated. High blood pressure, diabetes, and heart disease were included because chronic diseases and vascular risk factors are associated with poor health-related QoL [41, 42].

The MBI-C is a 34-item rating scale developed to measure symptoms in accordance with the MBI criteria. The MBI-C has been validated for completion by self, informant, or clinician, administered in person, by telephone, or online [43–47]; the self-report was used for this analysis [46]. MBI-C item scoring ranges from 0–3 with higher scores indicating greater symptom severity [43]. Total MBI severity score was calculated as the sum of all MBI-C item scores (range: 0–102). Participants were classified as having MBI (MBI+) using a validated cut-off score of ≥ 8, otherwise they were categorized as MBI- [48]. MBI domains have been shown to differentially associate with cognitive decline [49–51], and other health outcomes such as frailty and hearing loss [36, 43, 52] and thus, domain scores were generated. The decreased motivation and affective dysregulation domains each comprise 6 items (range: 0–18), the impulse dyscontrol domain comprises 12 items (range: 0–36), and the social inappropriateness and psychosis domains each comprise five items (range: 0–15) [43]. Domain specific prevalence was established using a cut-off score of ≥ 1.

QoL was measured using the EQ-5D and QFS-5, both self-reported. The EQ-5D measures QoL through the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [53]. Participants rate their QoL in each dimension on a scale from 1 to 5 with 1 indicating no problems in the respective area and five indicating discomfort or inability to perform activity. A sum of all five dimensions (range: 1–25) of the EQ-5D was used to calculate the total score, with greater scores indicating worse QoL. The QFS-5 provides a different and complementary perspective on QoL as it was developed with a focus on abilities and life engagement, with deliberate exclusion of any mental or physical health symptomatology in measuring QoL [54, 55]. The QFS-5 assesses the domains of productivity, self-care, leisure, relationships, and life satisfaction. Five questions in each of the five domains are scored on a scale of 0–3 (range: 0–75). The mean QFS-5 score was used for analysis, with higher values corresponding to higher QoL.

2.4 | Statistical Analysis

R version 4.3.2 was used to conduct all statistical analyses. Participant characteristics were summarized using means, standard deviation (SD), and ranges for numeric variables, and counts with percentages for categorical variables. Differences between MBI+ and MBI- in these characteristics were assessed using independent samples *t*-tests for numeric variables and chi square tests for categorical variables. As there is potential for self-selection bias, demographic comparisons were conducted between those who did and did not complete the relevant questionnaires required for this study.

Two separate multivariable linear regressions were used to model the association between MBI-C total score (predictor) and EQ-5D total score or QFS-5 mean score (outcomes). Models adjusted for age, cognition sex, education, ethnocultural origin (multi-select), marital status, employment status, high blood pressure, heart disease, and diabetes. To control for cognition in the models, the Everyday Cognition (Ecog II) scale [56] was used, with higher Ecog II scores indicating greater impairment. Linear regression assumptions were satisfied based on visual inspection of residual distributions in the EQ-5D analyses. For QFS-5 analyses, robust standard error (SE) values were applied to address heteroscedasticity. Both the EQ-5D total score and QFS-5 mean score were standardized to facilitate interpretation of the coefficients. A 90% winsorization, limiting extreme values to the 5th and 95th percentile thresholds, was used on the EQ-5D and QFS-5 total score variables to reduce the leverage of outliers on the statistical model without excluding them. A secondary analysis was conducted exploring associations between specific MBI domains and QoL. An MBI*sex interaction term was included in the models as part of secondary analyses to investigate potential sex differences. A sensitivity analysis was conducted removing anxiety and depression items from the EQ-5D total score to ensure that an observed association between MBI and EQ-5D could not be attributed to common items pertaining to symptoms of depression or anxiety.

3 | Results

3.1 | Sample Characteristics

Sample characteristics are found in Table 1. The age of participants was 64.4 $\pm$ 7.2 years (mean $\pm$ SD) and the number of years of education was 15.4 $\pm$ 4.2, with 79.4% of the sample being female. Among all participants, 48.7% identified having North American origins, 84.6% identified having European origins, and 71.1% of participants reported being married. The ECog-II score was 58.9 $\pm$ 15.8. Compared with participants excluded from the analysis (Figure 1), the included participants

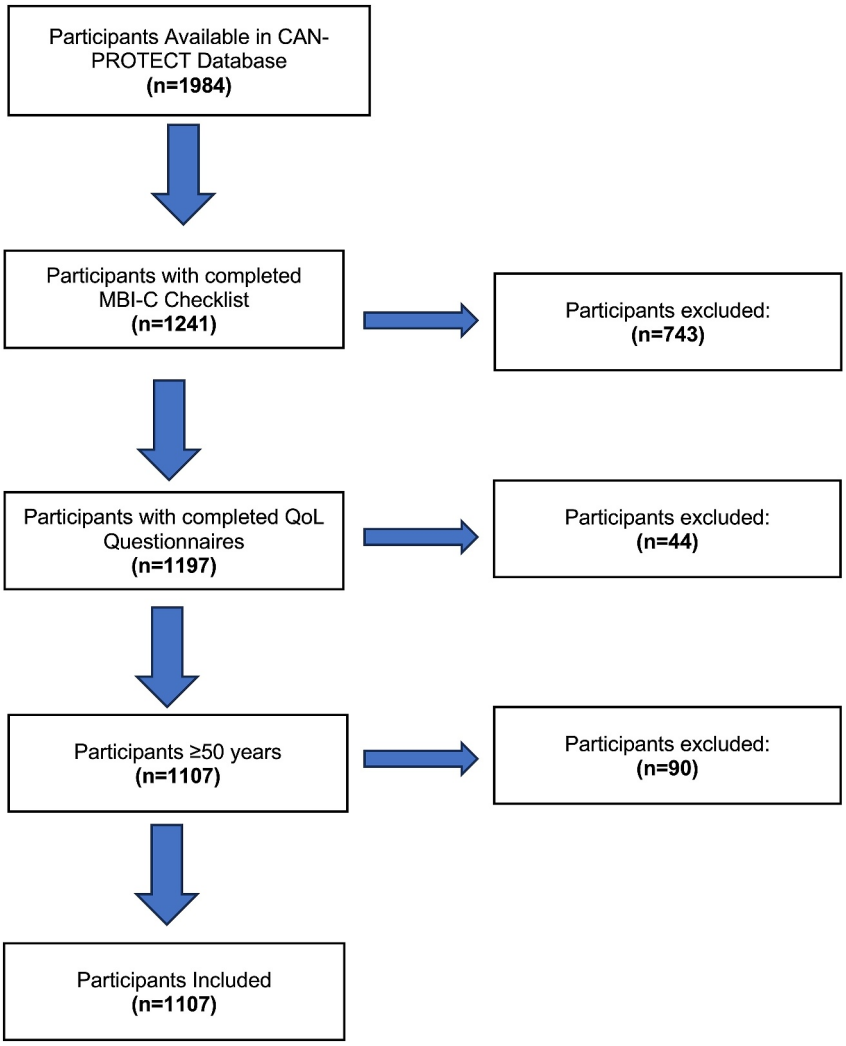

FIGURE 1 | Study flow describing inclusion and exclusion criteria for participants from the Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behavior, Function, and Caregiving in Aging (CAN-PROTECT). QoL, Quality of Life; MBI-C, Mild behavioral impairment checklist.

were more likely to be female but did not differ in cognition or years of education (Table 2).

From the entire sample of 1107 participants, 273 were classified as MBI+ (24.7%) and 834 as MBI- (75.3%). In the sample, total MBI-C score was 5.4 ± 7.6, EQ-5D score was 6.8 ± 1.7, and QFS-5 score was 2.6 ± 0.4. The MBI+ group had an overall MBI symptom score of 15.7 ± 8.9 and the MBI-group had an overall MBI symptom score of 2.0 ± 2.1. The MBI+ group was younger than the MBI- group and had lower education levels. However, there was no difference in sex between the MBI+ and MBI- groups.

The most endorsed MBI domain in the entire sample was affective dysregulation (54.6%), followed by impulse dyscontrol (51.1%), decreased drive and motivation (49.6%), abnormal perception or thought content (15.0%) and lastly, social inappropriateness (14.7%). Across MBI domains, severity was highest in decreased motivation and affective dysregulation and lowest in social inappropriateness and abnormal perception or thought content domains (Table 3).

3.2 | EQ-5D Analysis

Cross-sectional associations between MBI score and EQ-5D score in linear regression models are shown in Table 3. After adjusting for covariates, every 1-point increase in MBI total severity was associated with a 0.06 SD increase in EQ-5D score (95% confidence interval (CI): 0.05– 0.06, $p < 0.001$), indicating poorer QoL. The association was not moderated by sex (MBI*sex interaction term $\beta = -0.004$, 95% CI: −0.02 to −0.01, $p = 0.59$). Sensitivity analysis showed that even after removing anxiety/depression from the EQ-5D score, MBI was still significantly associated with poorer QoL ($\beta = 0.04$, 95% CI: 0.03–0.04, $p < 0.001$). Compared with MBI-, MBI+ status was associated with an EQ-5D score that was 0.86 SD higher (95% CI: 0.73–0.99).

Of all MBI domains, a 1-point increase in the abnormal perception or thought content domain was associated with the greatest SD change in EQ-5D ($\beta = 0.30$, 95% CI: 0.21–0.39, $p < 0.001$). This effect was followed by social inappropriateness ($\beta = 0.20$, 95% CI: 0.13–0.28, $p < 0.001$), affective dysregulation ($\beta = 0.18$, 95% CI: 0.16–0.20, $p < 0.001$) and decreased

TABLE 1 | Sample characteristics stratified by MBI status.

Variable	Total	MBI−	MBI+	*p*-value
n	1107	834	273	
Female sex (%)	879 (79.4)	662 (79.4)	217 (79.5)	1.00
Age (years)	64.4 (7.2); 50–89	65.0 (7.0); 50–89	62.5 (7.6); 50–82	< 0.001
ECog-II score	58.9 (15.8); 0–154	55.6 (13.5); 0–104	69.2 (18.0); 0–154	< 0.001
Education (years)	15.4 (4.2); 0–22	15.4 (4.2); 0–22	14.9 (4.0); 2–22	0.006
Ethnocultural origin (%)[a]				
North American	539 (48.6)	395 (47.4)	144 (52.7)	0.140
European	936 (84.6)	706 (84.7)	230 (84.2)	0.95
Caribbean	9 (0.8)	5 (0.6)	4 (1.5)	0.32
South American	4 (0.3)	3 (0.4)	1 (0.40)	1.00
African	8 (0.8)	6 (0.7)	2 (0.7)	1.00
Asian	22 (2.0)	18 (2.2)	4 (1.5)	0.64
Oceania	4 (0.4)	4 (0.5)	0 (0.0)	0.57
Marital status (%)				
Married	787 (72.2)	610 (73.1)	177 (64.8)	0.11
Widowed	64 (5.9)	48 (5.8)	16 (5.9)	
Separated	17 (1.6)	13 (1.6)	4 (1.5)	
Divorced	92 (8.4)	66 (7.9)	26 (9.5)	
Common-law	71 (6.5)	50 (6.0)	21 (7.7)	
Cohabitating	8 (0.7)	6 (0.7)	2 (0.7)	
Single	25 (2.3)	14 (1.7)	11 (4.0)	
Never married	42 (3.9)	26 (3.1)	16 (5.9)	
Prefer not to say	1 (0.1)	1 (0.1)	0 (0.0)	
Employment status (%)				
Employed (full-time)	213 (19.5)	142 (17.0)	71 (26.0)	< 0.001
Employed (part-time)	85 (7.8)	65 (7.8)	20 (7.3)	
Self employed	84 (7.7)	63 (7.6)	21 (7.7)	
Retired	712 (65.3)	559 (67.0)	153 (56.0)	
Unemployed	12 (1.1)	4 (0.5)	8 (2.9)	
Prefer not to say	1 (0.1)	1 (0.1)	0 (0.0)	
Unstandardized EQ-5D score	6.8 (1.7); 5–11	6.5 (1.3); 5–11	8.1 (1.8); 5–11	< 0.001
Unstandardized QFS-5 score	2.6 (0.4); 1–3	2.8 (0.2); 1.7–3	2.3 (0.4); 8–65	< 0.001
Total MBI-C score	5.4 (7.6); 0–65s	2.0 (2.1); 0–7	15.7 (8.9); 8–65	< 0.001
MBI domain scores				
Decreased drive and motivation (apathy) score	1.7 (2.6); 0–18	0.6 (1.0); 0–5	5.0 (3.1); 0–18	< 0.001
Affective dysregulation (mood and anxiety symptoms) score	1.7 (2.6); 0–16	0.7 (1.0); 0–7	5.0 (3.3); 0–16	< 0.001
Impulse dyscontrol (agitation, impulsivity, abnormal reward salience) score	1.5 (2.5); 0–20	0.6 (0.9); 0–5	4.3 (3.5); 0–20	< 0.001
Social inappropriateness (impaired social cognition) score	0.2 (0.8); 0–9	0.1 (0.3); 0–3	0.7 (1.3): 0–9	< 0.001
Abnormal perception or thought content (psychotic symptoms) score	0.2 (0.6); 0–5	0.1 (0.3); 0–2	0.6 (1.0); 0–5	< 0.001

(Continues)

TABLE 1 | (Continued)

Variable	Total	MBI−	MBI+	*p*-value
MBI prevalence Any MBI (≥ 8)	273 (24.7)			
MBI domain prevalence (≥ 1)				
Decreased drive and motivation (apathy)	549 (49.6)	282 (33.8)	267 (97.8)	
Affective dysregulation (mood and anxiety symptoms)	604 (54.6)	338 (40.5)	266 (97.4)	
Impulse dyscontrol (agitation, impulsivity, abnormal reward salience)	566 (51.1)	310 (37.2)	256 (93.8)	
Social inappropriateness (impaired social cognition)	163 (14.7)	59 (7.1)	104 (38.1)	
Abnormal perception or thought content (psychotic symptoms)	166 (15.0)	46 (5.5)	120 (44.0)	
Diagnoses	$n = 1090$	$n = 817$	$n = 273$	
High blood pressure (%)	81 (7.4)	211 (25.8)	92 (33.7)	0.01
Heart disease (%)	41 (3.8)	37 (4.5)	7 (26.0)	0.22
Diabetes (%)	303 (27.8)	51 (6.2)	30 (11.0)	0.01

Note: MBI status is determined by a cut-off of a score greater than or equal to 8 with MBI+ referring to those with MBI and MBI− referring to individuals without MBI. Numeric variables are shown in mean (SD); range and categorical variables are shown in *n* (%). To observe whether the difference between MBI+ and MBI− was significant, a chi square test was used for categorical variables and an independent samples *t*-test was used for numeric variables.
Abbreviations: ECog, Everyday Cognition; EQ-5D, EuroQol-5D; MBI, mild behavioral impairment; QFS-5, Quality of Life and Function Five Domain Scale; SD, standard deviation.
[a]May sum to greater than total number of participants because participants can select more than one ethnocultural origin.

TABLE 2 | Demographic comparison stratified by exclusion criteria.

Variable	Total	Included	Excluded	*p*-value
Participants (*n*)	1984	1107	877	
Female sex (%)	1542 (77.7)	879 (79.4)	663 (75.6)	< 0.001
Age (years)	62.7 (8.9); 40–91	64.4 (7.2); 50–89	60.6 (10.6); 40–91	0.40
ECog-II score	39.1 (31.0); 0–154	58.9 (15.8); 0–154	39.5 (30.6); 0–154	< 0.001
Education (years)	15.7 (6.0); 6–22	15.6 (4.2); 0–22	15.4 (4.4); 5–23	0.96

Note: Numeric variables are shown in mean (SD); range and categorical variables are shown in *n* (%). To observe whether the difference between included and excluded participants was significant, a chi square test was used for categorical variables and an independent samples *t*-test was used for numeric variables.
Abbreviation: ECog-II, Everyday Cognition.

motivation ($\beta = 0.14$, 95% CI: 0.12–0.16, $p < 0.001$). The smallest association with EQ-5D score was found in the impulse dyscontrol domain ($\beta = 0.11$, 95% CI: 0.09–0.14, $p < 0.001$).

3.3 | QFS-5 Analysis

In adjusted analyses, every 1-point increase in MBI total symptom score was associated with a 0.08 SD decrease in QFS-5 score (95% CI: −0.09 to −0.08, $p < 0.001$) (Table 3), indicating lower QoL. As per the MBI*sex interaction term, this association was found to be independent of sex ($p = 0.41$). Compared with MBI-, MBI+ status was associated with a QFS-5 score that was 1.22 SD lower (95% CI: −1.34 to −1.11).

Of all MBI domains, a 1-point increase in the abnormal perception or thought content was associated with the greatest change in SD ($\beta = -0.50$, 95% CI: −0.59 to −0.41, $p < 0.001$), followed by social inappropriateness ($\beta = -0.35$, 95% CI: −0.43 to −0.28, $p < 0.001$), decreased motivation ($\beta = 0.23$, 95% CI: −0.24 to −0.21, $p < 0.001$), and emotional dysregulation ($\beta = 0.23$, 95% CI: −0.24 to −0.21, $p < 0.001$). Like the EQ-5D analysis, the impulse dyscontrol domain was associated with the lowest SD change in standardized QoL measurement ($\beta = -0.19$, 95% CI: −0.21 to −0.18, $p < 0.001$).

4 | Discussion

This study found that in this sample of mostly cognitively normal older persons, those with greater MBI symptom severity reported poorer QoL compared to those with lower MBI symptom severity, independent of sex. Each MBI domain was linked to poorer QoL (Figure 2); abnormal perception or thought content had the strongest association, consistent with previous research [51, 57, 58]. Additionally, cognitive decline might serve as an indirect pathway through which psychosis affects QoL due to associations between cognitive impairment and poor QoL [31]. On the other hand, studies have linked psychosis to functional impairment and lower QoL, suggesting psychosis may interfere with wellbeing directly [59]. The impulse dyscontrol MBI domain had the weakest association with

TABLE 3 | Cross-sectional associations between MBI-C score and EQ-5D score/QFS-5 score in linear regression models.

Based on EQ-5D score	β	95% CI	*p*-value
Predictor			
Overall MBI score	0.06	0.05–0.06	< 0.001
Impulse dyscontrol (agitation, impulsivity, abnormal reward salience) score	0.11	0.09–0.14	< 0.001
Decreased drive and motivation (apathy) score	0.14	0.12–0.16	< 0.001
Affective dysregulation (mood and anxiety symptoms) score	0.18	0.16–0.20	< 0.001
Social inappropriateness (impaired social cognition) score	0.20	0.13–0.28	< 0.001
Abnormal perception or thought content (psychotic symptoms) score	0.30	0.21–0.39	< 0.001
Based on QFS-5 score			
Overall MBI score	−0.08	−0.09 to −0.08	< 0.001
Impulse dyscontrol (agitation, impulsivity, abnormal reward salience) score	−0.19	−0.21 to −0.18	< 0.001
Decreased drive and motivation (apathy) score	−0.23	−0.24 to −0.21	< 0.001
Affective dysregulation (mood and anxiety symptoms) score	−0.23	−0.25 to −0.21	< 0.001
Social inappropriateness (impaired social cognition) score	−0.35	−0.43 to −0.28	< 0.001
Abnormal perception or thought content (psychotic symptoms) score	−0.50	−0.59 to −0.41	< 0.001

Note: In all models, the predictor is either MBI score or MBI domain score. The outcome variable is the standardized EQ-5D score or QFS-5 score All models adjust for age, cognition, sex, education, ethnocultural origin, marital status, employment status, high blood pressure, heart disease, and diabetes. Estimated beta (β) coefficients represent the increase in worse quality of life for every unit increase in MBI score.
Abbreviations: CI, confidence interval; EQ-5D, EuroQol-5D; MBI, mild behavioral impairment; QFS-5, Quality of Life and Function Five Domain Scale.

poor QoL. Effects were large, compared to the variance of QoL in this generally healthy population.

Self-reported questionnaires on QoL can quantify contributing factors to individual life satisfaction, engagement, health, and fulfillment. Understanding QoL can also allow healthcare practitioners to assess the impact of medical diagnoses and inform interventions. In the context of dementia, QoL is an important health outcome because it can evaluate the effects of dementia on the patient's life [28]. Exploring QoL in advance of dementia is critical to understand disease progression. In persons without significant cognitive decline, assessing QoL can provide a baseline level, identify potentially modifiable stressors, and possibly prognosticate future trajectories. Furthermore, MBI symptoms have been associated with higher caregiver burden and poorer long-term functional outcomes, highlighting the importance of addressing these symptoms early on [60–62].

Previous studies have investigated the relationship between NPS and QoL in older adults living with dementia. In cross-sectional and longitudinal studies of both individuals with AD and nursing home residents, more behavioral disturbances in dementia were associated with lower QoL, progression to more severe stages of dementia, and increasing levels of depression, agitation and apathy [63–66]. One study showed that agitation, depression, anxiety, disinhibition, and irritability, but not cognitive symptoms, were associated with lower QoL [63]. Studies linking behavioral disturbances in dementia to lower QoL have sometimes used proxy measures [63], like the DEMQOL-proxy. With direct assessments of QoL in CAN-PROTECT, we extend this literature by showing that the NPS that constitute MBI are linked to worse QoL even in dementia-free persons at risk.

Generally QoL ratings do not differ between older males and females [67]. However, older males link QoL with physical function while older females tend to include feelings of discomfort; these differences may influence the results and interpretation of QoL studies [67]. A UK PROTECT study further demonstrated sex differences in the association between MBI and cognition, with greater effects in males, and recommendations to use sex as an effect modifier in analyses [35]. Our study finds no differences in the association between MBI and QoL in males and females. However, sex-dependent associations have been observed between MBI and other health-related outcomes [36, 52], warranting future studies of sex differences in MBI.

Our findings are consistent with a recent report of MBI and QoL in an outpatient clinic [33]. This Taiwanese study assessed 242 dementia-free older persons ≥ 50 years of age with normal cognition (n = 113) and amnestic MCI (n = 129). A clinical diagnosis of MBI was established using ISTAART criteria, and the Taiwanese version of the MBI-C. Higher informant-reported MBI-C total score, and decreased drive/motivation and affective dysregulation scores were associated with poorer self-reported QoL on the EQ-5D. However, a limitation of the EQ-5D in this context is that the inclusion of the anxiety/depression dimension may lead to a spurious association with MBI. The study further emphasized poorer QoL in those with MBI, with higher total MBI-C score and subscores compared to those without MBI.

Our study also enrolled dementia-free older adults who were mostly cognitively normal but not clinic based, serving as a complement to the previous study. It is important to look at community dwelling older adults outside of a clinical context as patients in clinical settings tend to have greater prevalence of NPS compared to persons in the community [68]. Furthermore, our analyses adjusted for cognition to assess the direct associations of behavior and QoL, and also included the novel QFS-5, with the similar results providing confidence in the findings.

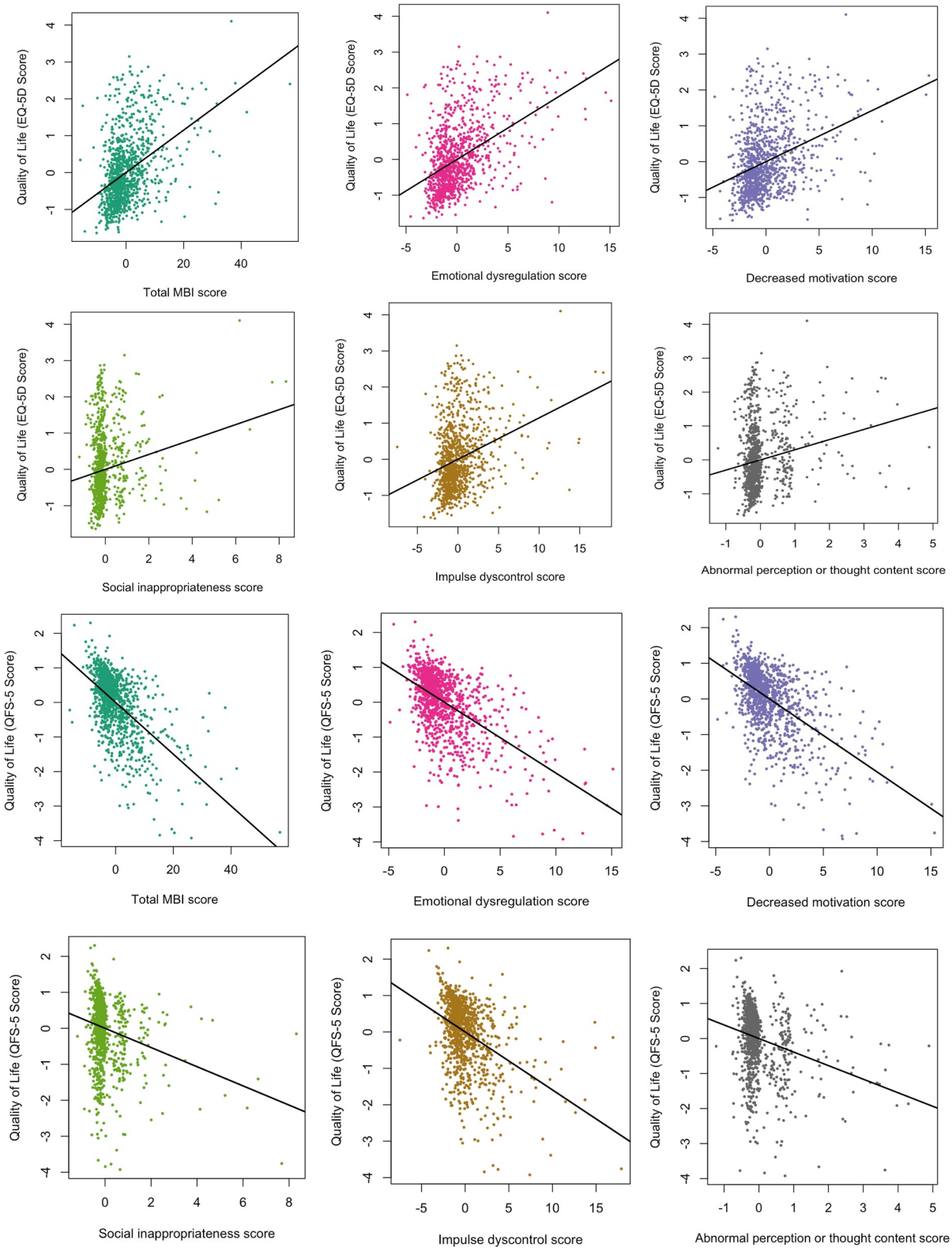

FIGURE 2 | Adjusted added variable plots for total mild behavioral impairment (MBI) symptom score, as measured by the mild behavioral impairment checklist (MBI-C) against standardized EuroQol-5D (EQ-5D) score, Quality of Life and Function Five Domain Scale (QFS-5) score and domain specific scores. The five MBI domains include decreased drive and motivation (apathy), affective dysregulation (mood and anxiety symptoms), impulse dyscontrol (agitation, impulsivity, abnormal reward salience), social inappropriateness (impaired social cognition), and abnormal perception or thought content (psychotic symptoms). The adjusted variable plots control for age, sex, cognition, education, ethnocultural origin, marital status, employment status, high blood pressure, heart disease, and diabetes.

In combination, both of these studies suggest that MBI, whether self- or informant-reported, is associated with poorer QoL. Furthermore, both studies indicate that understanding the relationship between MBI and QoL can potentially foster earlier therapeutic intervention, greater understanding of later-life emergent NPS, and the implications on individual lifestyles.

Mechanistically, the observed relationship between NPS and QoL can involve both direct and indirect pathways. NPS may directly lead people to perceive themselves as having a lower QoL. For example, even if an individual is relatively healthy, if they are constantly depressed, apathetic, anxious, or agitated, they may report lower QoL than someone less healthy who reports none of the behavioral problems. The EQ-5D would measure this directly, via the affective symptoms included in the scale. In contrast, the QFS-5, would measure this indirectly. Alternatively, and an a priori consideration during development of the QFS-5, other measures of mental health status could be included in models as covariates, mediators, or moderators, to better explore different contributions to QoL.

NPS can also indirectly affect QoL by exacerbating existing health/psychosocial conditions. QoL is linked with MBI, a dementia risk indicator, but QoL is also linked with modifiable risk factors in a patient's life such physical activity, diet and social interaction, which can interact and amplify the impact on the individual [65, 66]. For example, an older individual with late-onset depression may start to walk around less, thereby worsening their mobility, leading to lower QoL. However, causality can work in the opposite direction, as poor QoL might lead to MBI symptoms. Thus, future longitudinal studies can be used to show whether MBI predicts declining QoL or declining QoL predicts MBI.

As QoL is unique to the individual, the implications will vary from person to person [69]. Furthermore, due to the interconnectedness between NPS and progressing neurodegenerative disease, this constantly evolving relationship alters how the individual may interact with others and the environment, resulting in poorer QoL as symptoms worsen. A decline in a person's abilities attendant with neurodegenerative disease onset may influence how they perceive the burden and their functional capacity [69]. Further, MBI has also been linked to loneliness [70], which can affect QoL. Together, both our study and the Taiwanese study support direct and indirect pathways in the relationship between NPS and QoL, evident through the use of both self-reported and informant-reported QoL.

The large sample of participants in the present study ensured sufficient statistical power to investigate associations between global and domain-specific MBI symptom severity and QoL as measured by the EQ-5D and QFS-5. We addressed depression/anxiety items in the EQ-5D as a potential confounder for the observed MBI-QoL association by conducting a sensitivity analysis that excluded those items from the EQ-5D total score and by employing a novel measure of QoL (QFS-5) that excludes psychiatric symptoms from measurement of QoL. However, the cross-sectional nature of the data analyzed in the present study precludes investigation of causal mechanisms through which MBI may influence QoL and vice versa. Moreover, the inclusion of a higher proportion of females than males in the sample may have introduced bias into the study. To address this, future studies should aim to include representative proportions of males and females. In addition to looking at sex as a moderator, future studies should explore gender as well, to further understand and compare the relationship observed.

We did not assess possible social support associations with MBI and QoL, however, future studies should include these data given previous associations with QoL [71]. Another limitation of our study was inability to measure and compare the association in diverse cultures and different socioeconomic backgrounds. Future sampling and recruitment efforts will aim to address this issue. Lastly, future studies should consider both self- and study-partner-reported MBI and QoL to gain a more comprehensive understanding of the association with QoL, across diverse samples [72].

Nonetheless, it is important to identify NPS in older adults even in advance of dementia, and to include QoL in this work. Not only would this help with dementia prognostication by including another metric but could facilitate earlier interventions to improve QoL and standard of care for older adults. Earlier interventions are important because as neurodegenerative diseases progress, there are fewer preventative measures or modifiable risk factors that can be addressed to reduce the burden on the individual [66]. Further studies are required to determine if treatment of MBI can play a role in improving QoL, if management of MBI can reduce the progressive burden of neurodegenerative disease, and if QoL is a proxy marker of disease progression. These findings may inform early interventions at preclinical and prodromal stages of neurodegenerative disease that target mental and emotional health to improve QoL in older adult populations [63].

5 | Conclusion

In this sample of mostly cognitively unimpaired community dwelling older Canadians, we found MBI to be associated with poorer QoL, independent of sex. The EQ-5D and QFS-5 aligned with respect to measurement of QoL, demonstrating the utility of the QFS-5 and its feasibility for further use.

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Ethics Statement

Ethics approval for the study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB21-1065).

Conflicts of Interest

EES reported consulting (unpaid) for Alnylam Pharmaceuticals and Eli Lilly, and an advisory board (unpaid) for Eisai. ZI has served as an advisor/consultant to CADTH, Eisai, Lilly, Lundbeck/Otsuka, Novo Nordisk, and Roche.

Data Availability Statement

Data will be available upon reasonable request via corresponding author.

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