Received: 29 July 2023 | Revised: 1 November 2023 | Accepted: 21 April 2024

DOI: 10.1002/hsr2.2106

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Depression is associated with the nonmotor symptoms of Parkinson's disease: A comparative analysis

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Abstract

Background and aims: The nonmotor symptoms (NMS) of Parkinson's disease (PD) and their potential role in early diagnosis are recent debates. Herein, we aimed to investigate the association between depression and NMS of PD including sleep disorders, hyposexuality, hyposmia, constipation, and orthostatic hypotension.

Methods: A total of 93 PD patients with depression and 67 PD patients without depression were included in the study, and NMS were compared between the two groups. Furthermore, the possible associations between depression severity measured by Beck Depression Inventory (BDI) and NMS were investigated using linear regression or binary logistic regression models controlled for possible confounders. Eventually, we performed a subgroup analysis in each mild, moderate, and severe depression group.

Results: Orthostatic hypotension, constipation, and hyposexuality showed a significant difference between PD patients with and without depression ($p < 0.001$, $p = 0.029$, and $p < 0.001$, respectively). The BDI score was significantly associated with hyposexuality, Montreal cognitive assessment (MoCA), and Pittsburgh Sleep Quality ($p = 0.016$, $p = 0.010$, and $p = 0.011$, respectively); however, after adjustments for possible confounders, the associations of the BDI score with the MoCA score and hyposexuality remained significant ($p = 0.015$ and $p = 0.019$, respectively). Considering subgroup analysis, a similar pattern of significant results was observed particularly in the severe group.

Conclusions: This study suggests a possible association between depression in PD patients and some NMS observed in the course of PD. These findings could be beneficial for early diagnosis of the disease, which eventually could make a considerable difference in the management of PD patients. Additional interventional longitudinal studies are warranted to explore how controlling depression could impact the NMS of patients with PD.

Mahsa Mayeli and Mahan Shafie contributed equally to this study.

KEYWORDS
depression, nonmotor symptoms, Parkinson's disease

1 | INTRODUCTION

Early diagnostic and prognostic evaluation are crucial concerns in neurodegenerative diseases that have prompted many pursuits in proposing potential predictors.[1] As one of the most common progressive neurodegenerative disorders worldwide, mainly among the elderly population, Parkinson's disease (PD) is characterized by piecemeal loss and death of the substantia nigra pars compacta neurons and aggregation of the α-synuclein (α-syn) protein in the central nervous system.[2] This pathophysiology clinically manifests through common motor symptoms, including resting tremor, bradykinesia, gait difficulties, muscle rigidity, and postural instability, which interferes with activities of daily living.[3,4] Although PD is mainly known by motor symptoms, many nonmotor symptoms (NMS) are proposed to be associated with PD. Importantly, motor symptoms are usually associated with the advanced disease, while NMS could be utilized as early biomarkers of the disease even before the diagnosis of PD.[5]

The prevalence of depression among PD patients is about 40%, but because of overlapping symptoms of PD and depression, it could be primarily undiagnosed.[6] As disabling comorbidity in PD, depression is remarkably prevalent. This might be due to the potential involvement of joint neural microstructural pathophysiology between depression and PD.[7] Although the pathophysiological underpinnings are yet unclarified, the current literature strongly suggests that depression is indeed associated with PD,[8] and depression is also remarkably more prevalent in patients with PD compared with a normal population.[9]

Former works have suggested that at least one NMS manifests in PD patients.[6] Recently, different scales have been developed to assess NMS in PD, which contain various dimensions ranging from mood and cognitive impairment, sleep disturbances, and autonomic dysfunction (orthostatic hypotension) to gastrointestinal impairments and sexual dysfunction,[10–12] and some studies have been estimated the prevalence of NMS using these scales and concluded almost all patients with PD experience at least one NMS.[13] Sleep disorders prevalence is about 90% and some studies suggest that sleep disorder is connected with a higher risk of developing PD in the future.[14] NMS in PD patients have a vast unfavorable impact on Prognosis and the quality of life (QoL) in patients, such as faster motor and cognitive deterioration.[15] Despite their great impact on patients' QoL, clinical diagnosis challenges remain regarding the diagnosis of NMS, which is partly due to the dominance of other symptoms in PD. Therefore, determining clinical red flags of NMS could help with promoting a more thorough investigation of these symptoms in a certain group of patients. This is particularly of significance since the NMS of PD are known to precede the disease by years and detecting them might help earlier diagnosis.[8]

Despite the prevalence of depression and NMS among patients with PD, the possible relationship between them has been less investigated. Previous studies have reported that PD patients with depression were more likely to present with severe constipation. However, olfactory dysfunction appeared to be less associated with depression severity.[16] The association between depression and sleep disturbances have been also reported.[17]

As, NMS have been specifically noticed regarding their potential utility as diagnostic and prognostic tools for PD, herein, we aimed to investigate whether depression in patients with PD is associated with a range of NMS. We hypothesized that NMS are more common among PD patients with depression. Furthermore, we hypothesized that the severity of depression is associated with the presence of NMS in these patients. For this purpose, we primarily compared NMS between those PD patients with and without concurrent depression, and then, we evaluated the possible associations between depression severity and NMS. Eventually, we performed a subgroup analysis in each mild, moderate, and severe depression group.

2 | METHODS

2.1 | Design and participants

We reported this study according to the Strengthening The Reporting of OBservational studies in Epidemiology statement.[18] All patients referring to university referral clinics between March 2021 and December 2021 with a diagnosis of PD who gave their written informed consent were initially considered to be included in the study. After assessment for possible concurrent depression diagnosis, a total of 93 PD patients with depression and 67 PD patients without depression were eventually included in the study. Those with any other confirmed prior psychiatric disorder including anxiety disorders, bipolar disorder, schizophrenia, and substance abuse, or any other neurologic disorders including epilepsy, dementia, stroke, or head trauma were excluded.

2.2 | Measurements and definitions

The diagnosis of PD was confirmed by expert neurologists using the criteria developed by the UK Parkinson's Disease Society Brain Bank for the clinical diagnosis of PD.[19] The stage and the severity of the disease were determined using the Hoehn and Yahr scale.[20] Demographic information and clinical characteristics including PD duration, depression duration, PD medications, levodopa equivalate daily dose (LEDD), and depression medications were included. Patients with depression were evaluated by expert psychiatrists based on diagnostic criteria for the major depressive disorder of the

Diagnostic and Statistical Manual of Mental Disorders, fifth edition.[21] Depression severity was evaluated using Beck Depression Inventory (BDI),[22] which has been tested for validity and reliability in PD.[23] The BDI has been widely used as an assessment instrument for the intensity of depression in patients who meet clinical diagnostic criteria for depressive syndromes, in which, scores from 0 through 9 indicate no or minimal depression; scores from 10 through 18 indicate mild to moderate depression; scores from 19 through 29 indicate moderate to severe depression; scores from 30 through 63 indicate severe depression. The PD's NMS included hyposmia, orthostatic hypotension, constipation, hyposexuality, and sleep disturbances. Hyposmia was evaluated based on clinical history accompanied by testing the patients' sense of smell using three odorous substances, including coffee, cinnamon, and mint. A diagnosis of hyposmia was established if the patient was incapable of detecting two out of three odors. Orthostatic hypotension was also evaluated by a physician, clinically defined as a decrease in systolic blood pressure of 20 mmHg or more, and/or a decrease in diastolic blood pressure of 10 mmHg or more, within 3 min of standing compared with sitting or supine position. Constipation and hyposexuality were assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS) questionnaire as parts of autonomic dysfunction and patients report. Sleep quality was assessed using the Pittsburgh Sleep Quality (PSQ)[24] and Epworth sleepiness scale (ESS)[25] to investigate daytime sleepiness, and REM Sleep Behavior Disorder Sleep Questionnaire (RBDSQ)[26] was applied to investigate REM sleep disorders. Eventually, cognitive evaluation was conducted using Montreal cognitive assessment (MoCA).[27]

2.3 | Ethical considerations

The study proposal was evaluated ethically by the ethics committee of Tehran University of Medical Sciences and was approved with the ethics code of IR.TUMS.MEDICINE.REC.1398.455. The protocol of this study corresponded to the 2013 Helsinki declaration. All participants gave written informed consent and were considered anonymous and all data were registered confidentially with no personal information.

2.4 | Statistical analysis

Continuous variables were compared between groups using an independent-sample *t* test or Mann–Whitney *U* test after assessing for normality using the Shapiro–Wilk test. Categorical variables were compared between groups using Pearson's χ^2 test or Fisher's exact test when it was appropriate. The binary logistic regression model was applied to assess the association of binominal NMSs and BDI score, in which the estimated effect was reported as an odds ratio (OR) with a 95% confidence interval (CI). Associations between scale

TABLE 1 Demographics, clinical characteristics, and NMSs in study population.

Clinical characteristics	PD with depression (*N* = 93)	PD without depression (*N* = 67)	*p*
Age (years)	66.38 (8.21)	67.40 (7.15)	0.431
Gender (female)	30 (32.3%)	28 (41.8%)	0.216
Hoehn & Yahr	1.50 (0.53)	1.53 (0.52)	0.716
Hoehn & Yahr stages			0.681
1	38 (40.9%)	26 (38.8%)	
1.5	27 (29.0%)	19 (28.4%)	
2	19 (20.4%)	14 (20.9%)	
2.5	7 (7.5%)	8 (11.9%)	
3	2 (2.2%)	0 (0%)	
PD duration (years)	5.33 (4.74)	4.78 (3.26)	0.997
Depression duration (years)	6.80 (3.69)	–	–
LEDD	268.20 (143.52)	273.49 (150.82)	0.921
PD drug			0.251
Levodopa	65 (69.9%)	41 (61.2%)	
Levodopa + Pramipexole	28 (30.1%)	26 (38.8%)	
Depression drug			–
Serteraline	48 (51.6%)	–	
Bupropione	45 (48.4%)	–	
ESS score	7.77 (4.96)	7.91 (4.46)	0.586
ESS class			0.858
Lower normal	31 (33.3%)	20 (29.9%)	
Higher normal	40 (43.0%)	30 (44.8%)	
Mild excessive	10 (10.8%)	10 (14.9%)	
Moderate excessive	5 (5.4%)	4 (6.0%)	
Severe excessive	7 (7.5%)	3 (4.5%)	
PSQ score	11.10 (3.44)	11.55 (3.14)	0.418
RBDSQ score	8.00 (2.42)	8.13 (2.55)	0.779
MoCA score	20.29 (3.73)	20.82 (3.84)	0.289
BDI score	35.80 (12.15)	–	–
BDI class			–
Mild depression	11 (11.8%)	–	
Moderate depression	19 (20.4%)	–	
Severe depression	63 (67.7%)	–	
Hyposmia	28 (30.1%)	12 (17.9%)	0.079
Orthostatic hypotension	39 (41.9%)	7 (10.4%)	<0.001

(Continues)

TABLE 1 (Continued)

Clinical characteristics	PD with depression (*N* = 93)	PD without depression (*N* = 67)	*p*
Constipation	51 (54.8%)	25 (37.3%)	0.029
Hyposexuality	45 (48.4%)	11 (16.4%)	<0.001

Note: Data are presented as mean (SD) and number (%).

Abbreviations: BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; LEDD, levodopa equivalate daily dose; MoCA, Montreal Cognitive Assessment; NMSs, nonmotor symptoms; PD, Parkinson's disease; PSQ, Pain and Sleep Questionnaire; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire

non-motor variables and BDI score were also investigated by using the linear regression analysis. Variance inflation factor was considered in the adjusted regression model to determine any possible multicollinearity. Age, gender, PD duration, Hoehn and Yahr stage, and LEDD were considered probable confounders and adjusted in multivariate linear or logistic regressions. Data analyses were done using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp.). Statistical significance was considered as $p < 0.05$.

3 | RESULTS

In this study, 93 idiopathic PD patients with depression and 67 PD patients without depression were enrolled as the case and control groups, respectively. Among patients with depression, the mean BDI score for depression was 35.80: Eleven (11.8%) patients had mild depression, 19 (20.4%) patients had moderate depression, and 63 (67.7%) patients had severe depression according to the BDI questionnaire. The demographics and clinical characteristics of patients are detailed in Table 1. Demographics including age and gender were not significantly different between the two groups. Additionally, the two groups did not differ in Hoehn and Yahr stage, PD duration, and LEDD.

Our analysis did not yield a significant difference in the mean scores of the ESS, PSQ, RBDSQ, and MoCA ($p = 0.586$, 0.418, 0.779, and 0.289, respectively). Additionally, there was no significant difference between the two groups regarding the prevalence of hyposmia ($p = 0.079$). However, patients with depression showed significantly higher rates of orthostatic hypotension, constipation, and hyposexuality compared to the control group ($p < 0.001$, $p = 0.029$, and $p < 0.001$, respectively). Among the PD patients with depression, 41.9% of patients have experienced orthostatic hypotension, 54.8% of patients have reported constipation, and 48.4% of patients have reported hyposexuality, while these symptoms were reported in only 10.4%, 37.3%, and 16.4% of control subjects, respectively (Table 1).

Associations between demographics and NMS among patients with depression are shown in Tables 2 and 3. There was a positive significant correlation between ESS and Hoehn and Yahr staging ($p = 0.012$). PSQ score showed significant associations with Hoehn and Yahr staging, PD duration, depression duration, and LEDD ($p = 0.005$, 0.001, 0.030, and 0.001, respectively). BDI was also positively correlated with LEDD ($p = 0.030$). Additionally, orthostatic hypotension was associated with depression duration and LEDD ($p = 0.019$ and 0.038, respectively). Hyposexuality showed a significant association with gender ($p = 0.048$).

In the next step, the predictive value of the BDI score for NMSs in PD patients with depression was analyzed. The univariate regression analysis indicated that depression was significantly more severe in those with hyposexuality compared to those without this symptom ($p = 0.016$). Moreover, a significant negative association between the MoCA score and the BDI score ($p = 0.010$), and a significant positive association between the PSQ score and the BDI score ($p = 0.011$) were revealed. However, after adjusting for age, gender, PD duration, Hoehn and Yahr stage, and LEDD using multivariate regression analysis, the association of BDI score with the MoCA score and hyposexuality remained significant ($p = 0.0.015$ and $p = 0.0.019$, respectively) (Table 4).

The subgroup analyses were also performed to investigate the association between BDI score and nonmotor findings in mild, moderate, and severe depression groups (Figures 1 and 2). Among the PD patients with mild depression, BDI did not show a significant correlation with ESS, RBDSQ, PSQ, and MoCA scores ($p = 0.220$, 0.895, 0.775, and 0.626, respectively). Moreover, the BDI score was not associated with hyposmia, orthostatic hypotension, constipation, and hyposexuality ($p = 0.662$, 0.931, 0.329, and 0.133, respectively). A similar pattern was also yielded in the moderate depression group, and no significant association of the BDI score with non-motor scores was observed ($p = 0.270$, 0.770, 0.089, and 0.468, respectively). Similarly, the BDI score was not associated with NMS ($p = 0.573$, 0.310, 0.968, and 0.113, respectively). In the severe group, however, the MoCA score showed a significant negative association with the BDI score ($p = 0.042$), while other scores did not show any significant result ($p = 0.674$, 0.959, and 0.679, respectively). In this group, the BDI score was significantly higher in patients positive for orthostatic hypotension compared to the negative group ($p = 0.004$) and also in patients with hyposexuality compared to the negative group ($p = 0.028$). The BDI score did not differ in the hyposmia and constipation groups ($p = 0.901$ and 0.586).

4 | DISCUSSION

This study was conducted to explore the association between depression in patients with PD with other NMS, including sleep disorders, cognitive impairment, autonomic dysfunction, hyposexuality, constipation, and hyposmia. In summary, our study revealed significant differences in orthostatic hypotension, constipation, and hyposexuality between PD patients with and without depression. Even after accounting for potential confounding factors, the associations between BDI score, MoCA score, and hyposexuality remained significant. Subgroup analysis across mild, moderate, and

TABLE 2 Association between nonmotor scores and demographics in PD patients with depression.

Demographics	ESS		PSQ		RBSQ		MoCA		BDI	
	B	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*
Age	−0.031	0.770	−0.112	0.285	0.183	0.079	−0.169	0.105	−0.141	0.179
Gender	0.155	0.138	−0.068	0.518	0.010	0.928	0.184	0.077	−0.076	0.467
Hoehn and Yahr	0.259	0.012*	0.286	0.005*	−0.123	0.239	−0.141	0.177	0.144	0.169
PD duration	0.071	0.498	0.339	0.001*	0.110	0.294	−0.104	0.320	0.147	0.161
Depression duration	−0.005	0.963	0.255	0.030*	0.155	0.139	−0.116	0.270	0.039	0.708
LEDD	0.168	0.108	0.339	0.001*	−0.161	0.124	−0.140	0.181	0.226	0.030*

Abbreviations: B, standardized regression coefficient; BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; LEDD, levodopa equivalate daily dose; MoCA, Montreal cognitive assessment; NMS, nonmotor symptom; PD, Parkinson's disease; PSQ, Pain and Sleep Questionnaire; RBSQ, REM Sleep Behavior Disorder Screening Questionnaire.

*$p < 0.05$.

TABLE 3 Association between NMSs and demographics in PD patients with depression.

Demographics	Hyposmia		Orthostatic hypotension		Constipation		Hyposexuality	
	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Age	0.966	0.221	1.017	0.515	1.022	0.390	0.991	0.723
Gender	1.567	0.343	0.889	0.794	2.065	0.117	0.400	0.048*
Hoehn and Yahr	0.535	0.181	1.993	0.092	1.832	0.145	2.146	0.065
PD duration	0.980	0.690	1.069	1.154	1.110	0.059	1.026	0.569
Depression duration	0.926	0.239	1.153	0.019*	0.992	0.884	0.982	0.982
LEDD	0.999	0.727	1.003	0.038*	1.002	0.169	1.002	0.130

Abbreviations: LEDD, levodopa equivalate daily dose; NMS, nonmotor symptom; OR, odds ratio; PD, Parkinson's disease.

*$p < 0.05$.

TABLE 4 Prognostic value of BDI for prediction of NMSs in PD patients with depression.

Clinical outcomes	Unadjusted			Adjusted[a]		
	R^2	*B*	*p*	R^2	*B*	*p*
ESS score	0.001	0.036	0.731	0.088	0.002	0.986
PSQ score	0.069	0.263	0.011	0.209	0.173	0.087
RBDSQ	<0.001	0.007	0.944	0.129	0.067	0.523
MoCA	0.071	−0.266	0.010	0.167	−0.253	0.015
	Unadjusted			Adjusted[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
Hyposmia	1.008	0.972/1.046	0.671	1.007	0.968/1.047	0.720
Orthostatic hypotension	1.027	0.992/1/064	0.134	1.022	0.985/1.060	0.246
Constipation	1.010	0.976/1.044	0.577	1.003	0.967/1.041	0.864
Hyposexuality	1.045	1.008/1.083	0.016	1.048	1.008/1.090	0.019

Abbreviations: 95% CI, 95% confidence interval; B, standardized β coefficient; BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; LEDD, levodopa equivalate daily dose; MoCA, Montreal Cognitive Assessment; NMS, nonmotor symptom; OR, odds ratio; PD, Parkinson's disease; PSQ, Pain and Sleep Questionnaire; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire.

[a]Multivariate logistic regression adjusted for age, gender, PD duration, Hoehn and Yahr stage, and LEDD.

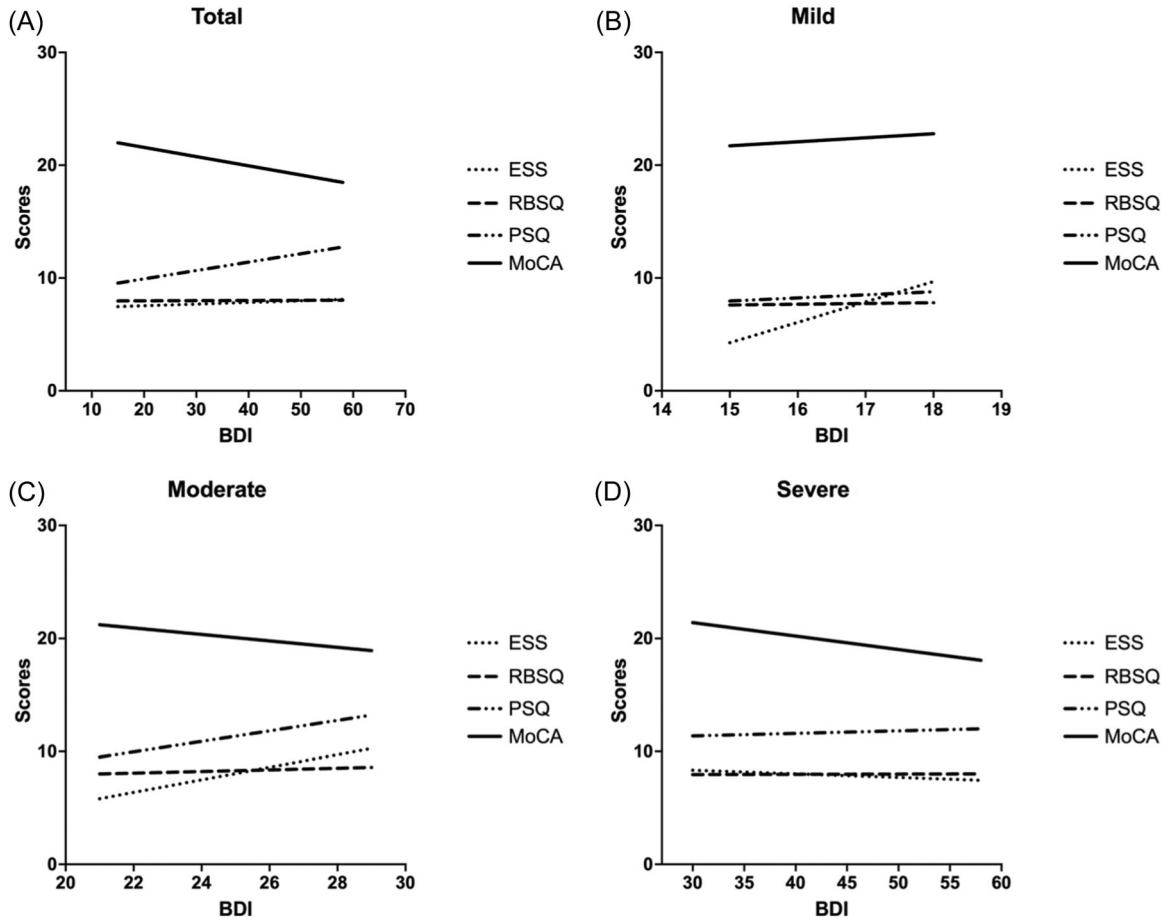

FIGURE 1 Association between Beck Depression Inventory (BDI) and nonmotor scores in (A) all Parkinson's disease (PD) patients with depression, (B) PD patients with mild depression, (C) PD patients with moderate depression, and (D) PD patients with severe depression.

severe depression groups showed consistent and significant results, particularly in the severe depression group.

It should be noted that the results of this study should be interpreted in light of some limitations. Our work found a significant association of depression score with sleep quality, cognitive performance, and hyposexuality, which were consistent with the former studies in this area. However, it is noteworthy that all three disturbed sleep quality, cognitive decline, and hyposexuality could be manifestations of both depression and PD; therefore, the exact relationship whether its causative or associative should be further investigated. Additionally, this study was conducted on a limited number of participants, and our findings might be related to the limited power to detect differences. Specifically, a large part of the studied population was severely depressed PD patients, which could affect the ultimate findings. Furthermore, this study was an observational cross-sectional study with known limitations for interpreting the results; thus, further studies with larger sample size and a longitudinal design are warranted to confirm and expand these observations.

In the past few years, a wide range of NMS from autonomic to cognitive impairments have been thoroughly scrutinized regarding their potential utility as diagnostic and prognostic tools for PD.[28,29] Studies have highlighted the high prevalence of NMS in PD patients and reported that almost all PD patients experienced at least one NMS during the disease, showing a pattern of fluctuation.[14] Some studies also indicate that non-motor dysfunction has a more significant impact on health-related QoL rather than motor abnormalities in patients diagnosed with PD.[30] The importance of early diagnosis through NMS is that by the time patient shows motor symptoms, more than 50% of striatal dopaminergic capacity is diminished.[31] Besides, PD diagnosis is more recently assessed for clinical research and diagnosis using criteria in which although motor abnormalities remain central, increasing recognition has been given to nonmotor manifestations.[32]

Although the primary pathology in PD is progressive dopaminergic denervation in the substantia nigra, other regions and neurotransmitters are also affected.[33] NMS are associated with neurotransmitters disturbance alongside dopamine deficiency in PD, and therefore, NMS and their severity might be associated with depression degree in PD patients. The high prevalence of depressive disorders in the early stages of the disease also confirms this hypothesis.[34] Additionally, depression has also been indicated by recent studies as a potential essential risk factor for developing PD in the future.[35] Different pathophysiology have been suggested that

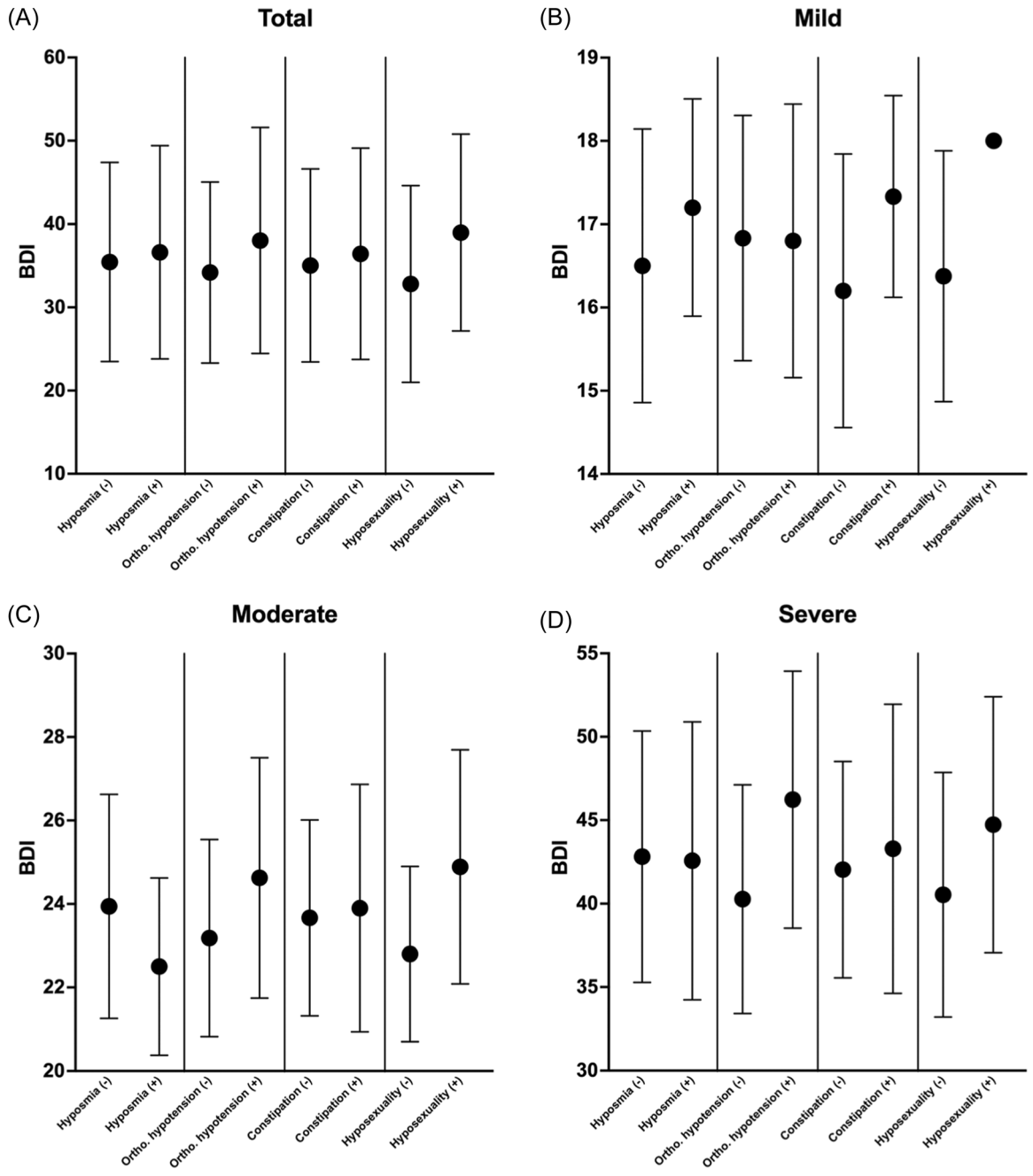

FIGURE 2 Association between Beck Depression Inventory (BDI) and nonmotor symptoms in (A) all Parkinson's disease (PD) patients with depression, (B) PD patients with mild depression, (C) PD patients with moderate depression, and (D) PD patients with severe depression.

could lead to depression as a prodromal symptom for PD, such as loss of dopamine and noradrenaline innervation in the limbic system,[36] disruption in serotonergic raphe nuclei in sporadic PD, and atrophic regions in cortical gyri and emotion recognition centers in depression-PD patients.[37,38] However, the exact etiology is yet not well understood.

In our study, there was no significant difference in MoCA score between patients with and without depression, however, our result showed a strong statistical relationship between cognitive impairment in PD patients with their depression severity. In our study sample, the majority of PD patients with depression were classified as severely depressed, while merely 12% of them were mildly depressed. More specifically, after subgroup analysis in each mild, moderate, and severe depression group, the association between cognitive decline and a higher depression score was only observed in the severe group, while it did not yield a significant result in the mild and moderate groups. This could justify why a strong negative association was found between BDI and MoCA scores in these patients. Cognitive deficit in PD patients ranges from mild cognitive impairment to dementia in the late stages[39] and is

suggested to be related to the accumulation of Lewi bodies in cortical regions and cholinergic dysfunction in the cortex.[40] Also, one of the early responses to the loss of dopamine in striae is rising dopamine levels in the prefrontal cortex which could harm cognitive function.[41] Other extranigral pathways such as dorsal serotonergic raphe, amygdala, hippocampal formation, and limbic thalamic nuclei with prefrontal projections are also simultaneously impaired in cognitive impairment and depression.[42] Current literature have investigated the ways in which mood disorders, specifically depression, could affect cognitive processes including attention, perception, interpretation, and memory.[43] On the other hand, based on recent studies, cognitive deficits can also lead to increased depression in patients with PD through deteriorating QoL.[44] Therefore, depression and cognitive impairment appear to be interrelated among patients with PD, which have been also suggested by our study.

No significant difference was observed in sleep scores between PD patients with and without depression. Among depressive group, ESS and RBDSQ were not associated with depression severity, and although PSQ showed a significant positive association with BDI score, it did not survive multiple adjustments for possible confounders. One of the earliest symptoms in PD patients is REM sleep disorders, which has been reported in about 90% of PD patients, manifested by insomnia, excessive daytime sleep (EDS), REM sleep without atonia, sleep-related breathing disorders such as obstructive sleep apnea, restless leg syndrome, and nocturia.[45] Some studies showed that neuronal damage and dysregulation of circadian molecules might lead to these symptoms.[46] Also, some works have suggested that interruptions in α-syn clearance by the glymphatic system might lead to sleep disorders and therefore fasten the progression of PD. Sleep also plays a significant role in cognitive and memorial functions and might therefore affect QoL in patients.[47] A previous study found a significant association of fatigue and EDS with motor symptoms, disease duration, depression, and dopaminergic treatment in patients with PD.[48] A study on the association between sleep disturbances and depression severity among patients with PD also reported that shorter total sleep time, sleeping less than usual, and insomnia severity were associated with depression severity in the total sample.[17]

In our research, orthostatic hypotension, constipation, and hyposexuality showed a significant difference between depressed and nondepressed groups. Furthermore, a statistically significant association was found between hyposexuality and patients' depression severity. Autonomic dysfunctions in PD patients consist of a vast spectrum, including cardiovascular, gastrointestinal, and sexual symptoms. Previous studies have reported a variety of factors from various medications to cognitive impairment that are associated with orthostatic hypotension in patients with PD.[49] There could be a mutual relationship between orthostatic hypotension and cognitive impairment, however, it is not exactly clear whether the relationship is causative.[50] From vascular aspect, some imaging studies suggested that repeated hypotension episodes might eventually lead to cerebral hypoperfusion, causing impaired cognition in PD patients.[51,52] Besides, pathological studies have proposed similar underlying bases corresponded to orthostatic hypotension and cognitive impairment affecting locus coeruleus region as the main region of norepinephrine production.[50,53] As there is a well-known close relationship between dopamine and sexual disorders,[54] hyposexuality is relatively common among patients with PD, associated with many factors including motor disabilities, autonomic dysfunction, sleep disturbances, pain, mood disorders, cognitive abnormalities, and medications.[55] However, hyposexuality and orgasmic dysfunction are often neglected because of patients' embarrassment and clinicians' focus on more apparent motor symptoms.[56] It should be noted that hyposexuality could be also related to depression medications such as selective serotonin reuptake inhibitors, which could specifically impact our results and interpretations. The high rates of constipation among PD patients are also concerning since gastroparesis and small intestine bacterial overgrowth can lead to malabsorption of PD medication in patients and, therefore, exacerbate motor symptoms.[57] Consistent with our findings, some studies are suggestive of an association between severe constipation and depression.[16] Olfactory dysfunction is one of the earliest NMS, which has been associated with a higher risk of PD progression, as it appears to be corresponded to early development of Lewy pathology and changes in neurotransmitters.[58] We did not find a significant difference in hyposmia between PD patients with and without depression. Moreover, no significant association was observed between hyposmia and depression severity, which was consistent with previous studies.[16]

One of the most critical debates in neurodegenerative diseases such as PD is early diagnosis, which allows us to initiate the proper management of the disease to prevent disease progression and further probable complications. Specifically, in the course of PD, since by the time of recognizable motor symptoms, the disease is already advanced, the early detection of NMS could be beneficial. This could result in an earlier diagnosis and treatment modification, which could make a considerable difference in QoL of PD patients. Hence, from a clinical perspective, our findings regarding the potential link between depression and other NMS could eventually lead to a considerable difference in the management of PD patients.

Due to limitations of our study, further research with a larger and more homogenous population with a longitudinal/interventional design are warranted to confirm and expand our observations. Additionally, the association between anxiety and depression has been well recognized, and evaluating the impact of each simultaneously on NMS in patients with PD could be further illustrative. Furthermore, some studies have shown heterogeneous and complex patterns of NMS fluctuations in patients with PD, which could be addressed in future studies.[59]

5 | CONCLUSION

In conclusion, our study suggests a possible association between depression in PD patients and some NMS observed in the course of PD. These findings could be beneficial for early diagnosis of the disease, which eventually could make a considerable

difference in the management of PD patients. Additional interventional longitudinal studies are warranted to explore how controlling depression could impact the NMS of patients with PD with different characteristics.

AUTHOR CONTRIBUTIONS

Mahsa Mayeli: Conceptualization; formal analysis; methodology; writing—original draft. **Mahan Shafie**: Conceptualization; formal analysis; methodology; writing—original draft. **Maryam Shiravi**: Conceptualization; data curation; methodology. **Tanin Adl Parvar**: Writing—original draft; writing—review and editing. **Zahra Mirsepassi**: Supervision; writing—review and editing. **Fatemeh Rahiminejad**: Supervision; writing—review and editing. **Reza Sattarpour**: Writing—original draft. **Vajiheh Aghamollaii**: Conceptualization; data curation; methodology; supervision; writing—review and editing.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study proposal was evaluated ethically at the ethics committee of Tehran University of Medical Sciences and was approved with the ethics code of IR.TUMS.MEDICINE.REC.1398.455. The protocol of this study corresponded to the 2013 Helsinki declaration. All participants gave written informed consent and were considered anonymous and all data registered confidentially with no personal information.

TRANSPARENCY STATEMENT

The corresponding author Vajiheh Aghamollaii affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Mayeli M, Shafie M, Shiravi M, et al. Depression is associated with the nonmotor symptoms of Parkinson's disease: a comparative analysis. *Health Sci Rep*. 2024;7:e2106. doi:10.1002/hsr2.2106