

# Association of Motor and Nonmotor Symptoms With Health-Related Quality of Life in a Large Online Cohort of People With Parkinson Disease

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## Abstract

### Background and Objectives

There is growing interest in health-related quality of life (HRQOL) as a comprehensive view of the patient's well-being, guiding concept for the treating clinician, and therapeutic trial outcome measure for patients with Parkinson disease (PwPD). The key determinants of HRQOL have not been investigated in large populations of PwPD. Our objective was to evaluate correlates of HRQOL in a large, online cohort of PwPD.

### Methods

As part of an ongoing online cohort study, we performed a cross-sectional analysis at enrollment of 23,058 PwPD. We conducted univariate and stepwise multivariate linear regression analyses of HRQOL as measured by the EQ-5D-5L tool. In addition, we performed an interaction analysis to evaluate heterogeneity of the effect of motor symptoms on HRQOL and Spearman correlation analysis to evaluate the association of nonmotor symptoms with HRQOL.

### Results

In the multivariate linear regression model, participants with moderate or severe depression, more severe motor symptoms, and a higher burden of medical comorbidities had the most substantially decreased HRQOL as measured by the EQ index ( $\beta$  -0.11, -0.18, -0.02, -0.01, respectively;  $p < 0.001$  for all). An interaction analysis showed that more severe motor symptoms had a higher effect on individuals with female sex, lower educational level, lower income, more severe depression, or more severe cognitive impairment ( $p \leq 0.01$  for interaction terms). Neuropsychiatric symptoms and falls had the most negative associations with HRQOL ( $\rho$  -0.31 to 0.37;  $p < 0.0001$ ).

### Discussion

Potentially treatable motor and nonmotor symptoms, particularly neuropsychiatric symptoms, account for a large amount of the variation in HRQOL in PwPD. Motor symptoms may have differential effects on HRQOL in different demographic and clinical subpopulations, highlighting important areas for future health disparities research. Our findings provide targets for clinician intervention and future research on symptom management to optimize HRQOL in PD.


### Classification of Evidence

This study provides Class II evidence that motor and neuropsychiatric symptoms are associated with HRQOL in PwPD.

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## Glossary

**GDS** = Geriatric Depression Scale; **HRQOL** = health-related quality of life; **IRB** = institutional review board; **MDS-UPDRS** = Movement Disorder Society–sponsored revision of the Unified Parkinson’s Disease Rating Scale; **NMS-Quest** = Nonmotor Symptom Questionnaire; **PD** = Parkinson disease; **PDAQ-15** = 15-item Penn Parkinson’s Daily Activities Questionnaire; **PwPD** = people with Parkinson disease; **SACQ** = Self-Administered Comorbidity Questionnaire.

Parkinson disease (PD) is a multisystem, progressive illness with a variable clinical presentation. There is no cure and the primary therapeutic focus is on symptom management; however, treatment can be incompletely effective or cause secondary complications. There is growing interest in health-related quality of life (HRQOL) as a comprehensive view of the patient’s well-being, guiding concept for the treating clinician, and clinical trial outcome measure for patients with neurodegenerative disease.<sup>1</sup> Understanding determinants of such a key yet at times unpredictable outcome is an essential first step to targeting its improvement.

Previous studies in selected populations demonstrate the importance of motor and increasingly nonmotor symptoms on HRQOL for people with PD (PwPD).<sup>2-4</sup> However, PD is heterogeneous and there may be differential effects of these symptoms in demographic and clinical subpopulations. Preliminary evidence suggests that HRQOL in PD varies by sex,<sup>5,6</sup> disease stage,<sup>7</sup> and proximity to an urban center.<sup>8,9</sup> Prior research has shown the overall importance of nonmotor symptoms on HRQOL,<sup>2</sup> but nonmotor symptom summary scales often have a limited interpretation as they encompass a large variety of symptoms with varying effect. PD is also associated with substantially increased economic burden,<sup>10</sup> which may interact in complex ways with HRQOL. The contributors to HRQOL have not been fully characterized in a large population of PwPD.

Fox Insight is a large online cohort study designed to assess the lived experience of people with PD. The sample size, geographic diversity, and wealth of participant-reported measures enable a more granular analysis of HRQOL in PD. We therefore investigated the key determinants of HRQOL in PD with a particular focus on possible disparities in different demographic and clinical subpopulations, the effect of individual nonmotor symptoms, and an exploration of markers of economic burden. Our primary research question is whether motor, nonmotor, and economic factors are associated with HRQOL in PwPD.

## Methods

### Population

We examined baseline data from participants with PD enrolled between 2017 and 2020 in the Fox Insight study. A full description of the Fox Insight study has been published previously.<sup>11</sup> Participants were recruited through in-person efforts (clinician referrals and events to promote research) and

digital channels (social network advertisements, email newsletters, and search engine marketing). Digital promotion strategies were used to increase participation in populations traditionally underrepresented in research.<sup>12</sup> PwPD underwent routine longitudinal assessments through an online survey platform regarding their overall health, lifestyle, motor symptoms, nonmotor symptoms, socioeconomic situation, and quality of life. We excluded individuals who initially reported a diagnosis of PD that was later revised to a different diagnosis and those who did not complete the quality of life assessment.

### Standard Protocols, Registrations, and Patient Consents

Participants provided informed consent through the Fox Insight website. Protocols were approved by the New England institutional review board (IRB) (IRB: 120160179; Legacy IRB: 14–236; sponsor protocol number: 1; study title: Fox Insight).

Data used in the preparation of this article were obtained from the Fox Insight database (initially on April 11, 2019, and updated on March 12, 2020). Up-to-date information on the study is available online.<sup>13</sup>

### Measures

#### Health-Related Quality of Life

Quality of life was ascertained by the EQ-5D-5L tool, a well-validated measure using 3 levels of severity to measure 5 dimensions of health.<sup>14</sup> We then converted the total score to an index based on US population norms.<sup>15</sup> The index is defined as 1 for best quality of life, 0 for a state equivalent to death, and negative values up to –1 corresponding to a state worse than death. The Movement Disorder Society recommends the use of this HRQOL assessment because it is well-validated and responsive to change in PD.<sup>16-18</sup>

#### Clinical Measures

Participants reported motor function by completing the Movement Disorder Society–sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part II.<sup>19</sup> The Nonmotor Symptom Questionnaire (NMS-Quest) was used to assess nonmotor symptoms.<sup>20</sup> We assessed depression with the modified (15-question) Geriatric Depression Scale (GDS).<sup>21</sup> Using validated cutoffs for the short assessment, scores <5 indicate no depression, 5–8 mild symptoms, 9–11 moderate symptoms, and 12–15 severe symptoms. Medical comorbidities were assessed by the Self-

Administered Comorbidity Questionnaire (SACQ), which queries the respondent about 14 health conditions and generates a score based on whether treatment is needed and if activities are limited by that diagnosis.<sup>22</sup> We used the Penn Parkinson's Daily Activities Questionnaire (PDAQ-15), a 15-item measure of instrumental activities of daily living yielding a score of 0 (worst) to 60 (best) that correlates well with global cognition across the disease stage, to measure cognitive function.<sup>23</sup> A previously validated cutoff of <43 was utilized to distinguish participants with normal or mildly impaired cognitive function from those with more severe impairment.<sup>23</sup> This cutoff was validated for this measure completed by knowledgeable informants and was used in this study as there is no currently validated measure for self-report.

### Other Variables

PwPD self-reported demographic variables (age, sex, race, income, educational level) and disease duration.

### Statistical Analysis

Summary statistics were used to describe the variables using means and SD for continuous variables, medians and interquartile ranges for continuous variables with skewed distributions, and counts and percentages for categorical data. Statistical significance was set at  $p < 0.05$ . All statistical analyses were conducted using Stata/SE 14.2 (StataCorp).

We conducted univariate and backwards stepwise multivariate linear regression to evaluate determinants of quality of life. The confounding factors age, sex, race, and years with PD were always included in the model. Candidate variables included motor symptoms (MDS-UPDRS part II), depression (GDS), cognitive function (PDAQ-15), medical comorbidities (SACQ), educational level, and income. To evaluate the variation in effect of motor symptoms, we performed an interaction analysis that was specified a priori between motor score and sex, race, disease duration, annual income, educational level, cognitive status, and depression severity.

We then divided nonmotor symptoms into categories based on the NMS-Quest. Neuropsychiatric symptoms included paranoia, hallucinations, disinterest, sad mood, decreased concentration, anxiety, and forgetfulness. Sensory symptoms included diplopia, pain, and anosmia. Gastrointestinal symptoms included bowel incontinence, dysphagia, weight loss, nausea, sialorrhea, incomplete emptying, and constipation. Sleep symptoms included sleepiness, restless legs syndrome, insomnia, vivid dreams, and dream enactment. Autonomic symptoms included falls, dizziness, sweating, sexual dysfunction, change in sexual interest, urinary frequency, and nocturia. For the purposes of our analysis, we considered a participant to be symptomatic in a category if he or she reported any symptom in that category. We then performed a Spearman correlation analysis to evaluate the mean difference in EQ index score between symptomatic and asymptomatic PwPD by each nonmotor symptom category and individual nonmotor symptom.

In a subcohort of PwPD who completed an additional survey on economic burden, we performed an exploratory analysis. We conducted univariate linear regression analysis of the correlation between economic markers (type of diagnosing provider, living location, insurance status, employment status, and hours of daily care) and EQ index. We then conducted a multivariate stepwise linear regression analysis of economic variables where we controlled for forced variables (age, sex, race, and years with PD) and candidate variables that reached criteria for statistical significance in the main analysis (MDS-UPDRS part II, GDS, PDAQ-15, SACQ, educational level, and income).

### Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

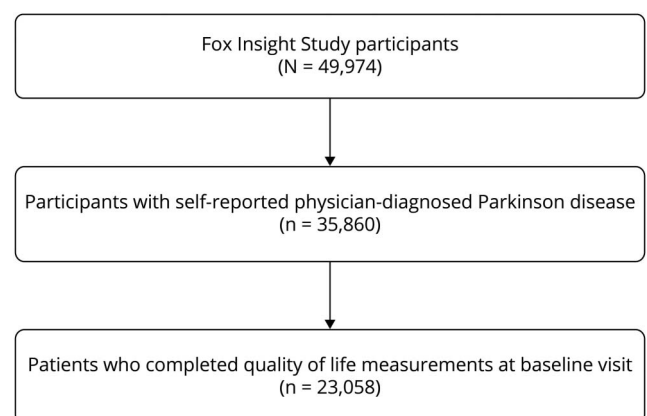
## Results

### Participant Characteristics

The sample selection of our cohort is outlined in Figure 1. At the time of this analysis, the Fox Insight study included 49,974 participants. Of the 35,860 individuals reporting a diagnosis of PD at baseline, 23,058 completed the HRQOL measurements and are included in this analysis. Compared with PwPD who completed the HRQOL assessment, those who did not complete the HRQOL assessment at baseline were slightly younger (mean 65.3 compared with 66.2 years;  $p < 0.0001$ ), had longer duration of PD (62% with >3 years of disease duration compared with 52%;  $p < 0.0001$ ), and were more likely to report nonwhite race (6% vs 4%;  $p < 0.0001$ ).

Demographic and clinical characteristics of the full analysis cohort ( $n = 23,058$ ) are summarized in Table 1. Descriptive statistics of the clinical scales are displayed in eTable 1 ([links.lww.com/WNL/B941](https://www.lww.com/WNL/B941)).

**Figure 1** Sample Selection of the Analysis Cohort



**Table 1** Demographic Characteristics of the Online Cohort (n = 23,058)

Characteristic	Mean ± SD or n (%)
Age, y	66.2 ± 9.7
Female	10,125 (44)
Race	
White	22,093 (95.8)
African American	166 (0.7)
Native American	225 (1.0)
Asian	383 (1.7)
Pacific Islander	23 (0.10)
No response	168 (0.73)
Years with PD	
0–3	11,188 (48.5)
3–10	8,484 (36.8)
11–50	3,347 (14.5)
Prefers not to answer	27 (0.12)
Missing	12 (0.00)
Self-reported comorbidity score	4.2 ± 3.8
Education	
High school	2,602 (11.3)
Some college	4,293 (18.6)
College degree	8,453 (37.0)
Advanced degree	7,639 (33.1)
Prefers not to answer	71 (0.3)
Missing	0
Income, USD	
<35,000	3,740 (18.6)
35,000–100,000	9,655 (48.1)
>100,000	6,678 (33.3)
Prefers not to answer	0
Missing	2,985 (12.9)
Employment	
Full time	4,480 (19.5)
Part time	1,685 (7.3)
Retired	15,422 (67.0)
Unemployed	1,310 (5.7)
Prefers not to answer	128 (0.56)
Missing	33 (0.00)

**Table 1** Demographic Characteristics of the Online Cohort (n = 23,058) (continued)

Characteristic	Mean ± SD or n (%)
Depression	
None (GDS <5)	13,420 (62.3)
Mild (GDS 5–8)	4,691 (21.8)
Moderate (GDS 9–11)	1,912 (8.9)
Severe (GDS 12–15)	1,524 (7.1)
Missing	1,511 (0.07)
Cognitive function	
Normal/MCI (PDAQ-15 >43)	17,872 (81.3)
Moderate–severe impairment (PDAQ-15 <43)	4,114 (18.7)
Missing	

Abbreviations: GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; PD = Parkinson disease; PDAQ-15 = Penn Parkinson's Daily Activities Questionnaire.

## Predictors of HRQOL

HRQOL in the sample was overall high with an average EQ index of 0.7 (±0.24). Results of univariate and multivariate linear regression analyses of the EQ index are summarized in Table 2. In univariate analysis, statistically significant predictors of the EQ index included sex ( $\beta$  -0.01), race ( $\beta$  -0.05), years with PD ( $\beta$  -0.07 for 3–10 years and -0.17 for 11–50 years compared with 0–3 years), SACQ score ( $\beta$  -0.03), MDS-UPDRS II score (-0.02), depression ( $\beta$  -0.16 for mild, -0.27 for moderate, and -0.42 for severe compared with none), more severe cognitive impairment ( $\beta$  -0.26), income ( $\beta$  0.12 for \$35,000–99,999 and 0.18 for >\$100,000 annual income compared with <\$35,000), and educational level ( $\beta$  0.05 for some college, 0.10 for college degree, and 0.13 for advanced degree compared with high school or less). In multivariate analyses, all candidate variables met statistical criteria for inclusion in the model ( $p < 0.05$ ). Severe depression had the largest correlation with quality of life in the fully adjusted model ( $\beta$  -0.18), followed by moderate depression ( $\beta$  -0.11), mild depression (-0.06), and income ( $\beta$  0.02 for both \$35,000–\$99,999 and >\$100,000 annual income compared with <\$35,000). MDS-UPDRS part II score ( $\beta$  -0.02) and SACQ score ( $\beta$  0.01) had a moderate contribution to HRQOL per point change. The multivariate model accounted for 62% of the variance of HRQOL as measured by the EQ index.

The results of the interaction analysis evaluating the effect of motor symptoms on HRQOL by subgroup are summarized in Figure 2. More severe motor symptoms exerted a significantly larger negative effect on HRQOL on individuals with female sex, lower educational level, lower income, more severe depression, or more severe cognitive impairment ( $p < 0.05$  for all).

**Table 2** Results From Univariate and Multivariate Linear Regression With the EQ-5D Index

Predictor	Univariate		Multivariate	
	$\beta$ coefficient (95% CI)	<i>p</i> Value	$\beta$ coefficient (95% CI)	<i>p</i> Value
Age	-0.00 (-0.00, -0.00)	0.224	0.00 (0.00, 0.00)	<0.001
Female sex	-0.01 (-0.02, -0.01)	<0.001	-0.02 (-0.03, -0.02)	<0.001
Nonwhite race	-0.05 (-0.07, -0.03)	<0.001	-0.00 (-0.01, 0.01)	0.648
<b>Years with PD</b>				
0-3	Ref	<0.001	Ref	0.0009
3-10	-0.07 (-0.07, -0.06)		-0.01 (-0.01, -0.04)	
11-50	-0.17 (-0.18, -0.16)		-0.01 (-0.01, 0.00)	
SACQ score	-0.03 (-0.03, -0.03)	<0.001	-0.01 (-0.01, -0.01)	<0.001
MDS-UPDRS II	-0.02 (-0.02, -0.02)	<0.001	-0.02 (-0.02, -0.02)	<0.001
<b>Depression</b>				
None (GDS <5)	Ref	<0.001		<0.001
Mild (GDS 5-8)	-0.16 (-0.17, -0.16)		-0.06 (-0.06, -0.05)	
Moderate (GDS 9-11)	-0.27 (-0.28, -0.26)		-0.11 (-0.11, -0.09)	
Severe (GDS 12-15)	-0.42 (-0.43, -0.41)		-0.18 (-0.19, -0.17)	
Moderate-severe cognitive impairment (PDAQ-15 <43)	-0.26 (-0.27, -0.21)	<0.001	-0.01 (-0.02, -0.01)	0.015
<b>Income, USD</b>				
<34,999	Ref	<0.001		<0.001
35,000-99,999	0.12 (0.11, 0.13)		0.02 (0.02, 0.03)	
>100,000	0.18 (0.18, 0.19)		0.02 (0.02, 0.03)	
<b>Education level</b>				
High school or less	Ref	<0.001		0.0044
Some college	0.05 (0.04, 0.06)		0.01 (0.01, 0.02)	
College degree	0.10 (0.09, 0.11)		0.01 (0.01, 0.02)	
Advanced degree	0.13 (0.12, 0.14)		0.01 (0.00, 0.02)	

Abbreviations: GDS = Geriatric Depression Scale; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD = Parkinson disease; PDAQ-15 = Penn Parkinson's Daily Activities Questionnaire; SACQ = Self-Administered Comorbidity Questionnaire.

## Nonmotor Symptom Prevalence and Association With HRQOL

Nonmotor symptom prevalence and Spearman correlation coefficients with HRQOL are summarized in Table 3. Sleep-related symptoms had the highest prevalence, with 86% of participants reporting at least 1 symptom in this category. A majority of participants also endorsed gastrointestinal (81%) or neuropsychiatric (80%) symptoms. Commonly reported individual symptoms included nocturia (72%), urinary frequency (68%), insomnia (64%), constipation (54%), and dizziness (47%).

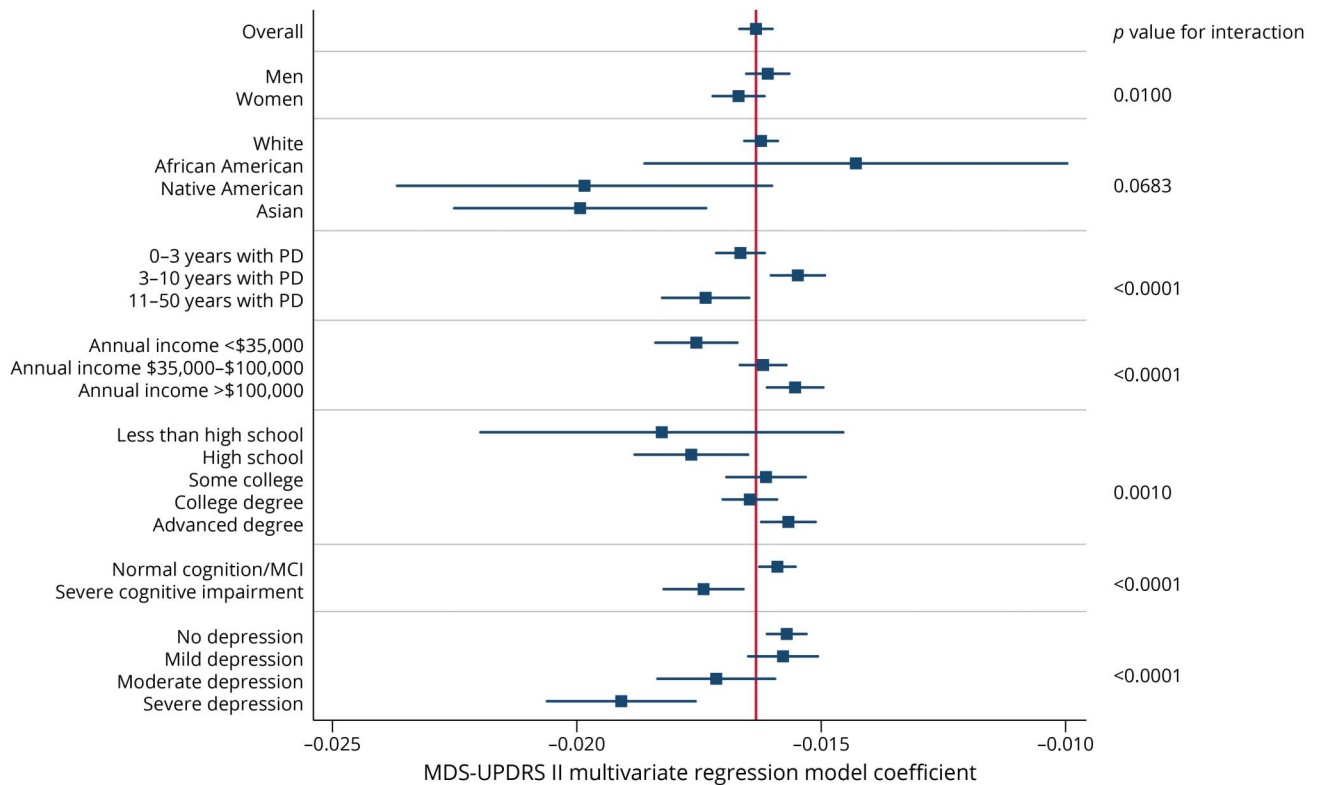
Of nonmotor symptoms categories, neuropsychiatric symptoms were the most negatively correlated with HRQOL ( $\rho$  -0.33,  $p$  < 0.0001). Of neuropsychiatric symptoms, sad

mood (54%) and forgetfulness (50%) were the most common. Of individual symptoms, disinterest ( $\rho$  -0.37), sad mood ( $\rho$  -0.36), decreased concentration ( $\rho$  -0.33), falls (-0.33), and anxiety (-0.31) were the most negatively correlated with HRQOL.

## Economic Predictors of HRQOL

In univariate linear regression analyses of HRQOL over economic factors, worse participant HRQOL was significantly correlated with diagnosis by a non-neurologist or primary provider, uninsured status, unemployment, and increased hours of daily care. After adjusting for all variables that met statistical criteria for inclusion in our main model, only increased hours of daily care remained statistically significant (Table 4).

**Figure 2** Heterogeneity Analysis of the Effect of Motor Symptoms (MDS-UPDRS Part II) on HRQOL (EQ Index)



Coefficients and CIs from the multivariate regression model are stratified by subgroup with corresponding results from an interaction analysis. In the multivariate model, we controlled for age, sex, years with Parkinson disease (PD), Self-Administered Comorbidity Questionnaire score, depression, more severe cognitive impairment, income, and educational level if not stratifying by that variable. HRQOL = health-related quality of life; MCI = mild cognitive impairment; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale.

### Classification of Evidence

This study provides Class II evidence that motor and neuropsychiatric symptoms are associated with HRQOL in PwPD.

### Discussion

The online design and rich array of patient-reported outcomes included in the Fox Insight study enabled us to perform a novel analysis of the demographic, clinical, and economic associations with HRQOL in the largest available cohort of PwPD. Our finding that more severe depression and motor symptoms had large negative correlation with HRQOL illustrates the importance of potentially treatable symptoms in driving this outcome. Our study also illustrates the greater effect of motor symptoms in PwPD who are female, have depression and cognitive decline, and have lower educational level and income. Sleep-related, gastrointestinal, and neuropsychiatric symptoms were highly prevalent nonmotor symptoms. Apathy, sad mood, anxiety, decreased concentration, and falls are likely impactful targets for clinical intervention and warrant additional high-quality research on optimal treatments.

The minimal clinically significant difference in the EQ index has not been specifically studied in PD, but is estimated to be

0.05–0.084 for patients with multiple sclerosis,<sup>24</sup> 0.10 for patients with stroke,<sup>25</sup> and 0.07–0.09 for patients with cancer.<sup>26</sup> Our regression coefficients for moderate and severe depression exceed these minimum differences. A change in MDS-UPDRS II score of approximately 5 points (–0.016 per point) and a change in SACQ score of 5 points (–0.011 per point) also meet this threshold, indicating that moderate changes in motor symptoms and medical comorbidities are likely to have a substantial effect on HRQOL.

Our results further elucidate the effect of motor symptoms, which have exhibited a variable relationship to HRQOL in prior studies, likely due to differences in ascertainment and sampling.<sup>27,28</sup> Motor symptoms as quantified by the UPDRS II have previously been established as determinants of worse HRQOL.<sup>7,29,30</sup> In particular, motor fluctuations,<sup>3</sup> nocturnal akinesia,<sup>31</sup> freezing,<sup>32</sup> and gait and balance impairment<sup>7,33</sup> are particularly bothersome to patients. Accordingly, medications that primarily target motor symptoms lead to improvement in quality of life.<sup>34</sup> In addition to confirming this association, we also found novel evidence of differential effects of motor symptoms on HRQOL in demographic and clinical subpopulations. From our analysis, we cannot conclude whether motor symptoms are more bothersome in these populations due to underlying disease state, differential treatment effects,

**Table 3** Results of Spearman Correlation Analysis of HRQOL (EQ Index) and Nonmotor Symptoms as Assessed by the NMS-Quest-PD Tool

Nonmotor symptom	Prevalence, %	$\rho$	$p$ Value
<b>Neuropsychiatric</b>	80	-0.33	<0.0001
Paranoia	4	-0.22	<0.0001
Hallucinations	12	-0.24	<0.0001
Disinterest	38	-0.37	<0.0001
Sad mood	54	-0.36	<0.0001
Decreased concentration	48	-0.33	<0.0001
Anxiety	39	-0.31	<0.0001
Forgetfulness	50	-0.27	<0.0001
<b>Autonomic</b>	47	-0.06	<0.0001
Falls	21	-0.33	<0.0001
Dizziness	47	-0.25	<0.0001
Sweating	24	-0.19	<0.0001
Sexual dysfunction	38	-0.20	<0.0001
Change in sexual interest	35	-0.19	<0.0001
Urinary frequency	68	-0.20	<0.0001
Nocturia	72	-0.10	<0.0001
<b>Sleep</b>	86	-0.21	<0.0001
Daytime sleepiness	21	-0.21	<0.0001
RLS	48	-0.27	<0.0001
Insomnia	64	-0.19	<0.0001
Vivid dreams	35	-0.15	<0.0001
Dream enactment	33	-0.14	<0.0001
<b>Gastrointestinal</b>	81	-0.25	<0.0001
Bowel incontinence	13	-0.19	<0.0001
Dysphagia	30	-0.27	<0.0001
Weight loss	12	-0.18	<0.0001
Nausea/vomiting	21	-0.20	<0.0001
Sialorrhea	28	-0.19	<0.0001
Incomplete emptying	44	-0.20	<0.0001
Constipation	54	-0.19	<0.0001
<b>Sensory</b>	61	-0.27	<0.0001
Pain	36	-0.26	<0.0001
Diplopia	17	-0.21	<0.0001
Anosmia	33	-0.16	<0.0001
<b>Other</b>		-0.25	<0.0001
Swelling	20	-0.25	<0.0001

Abbreviations: HRQOL = health-related quality of life; NMS-Quest-PD = Nonmotor Symptom Questionnaire-Parkinson disease; RLS = restless legs syndrome.

or differences in perception. Previous research has shown that women are less likely to undergo deep brain stimulation surgery compared with men<sup>35</sup> and individuals receiving care for PD at a public hospital are less likely to self-report exercise or physical therapy despite equivalent clinical severity.<sup>36</sup> As many motor symptoms are treatable with dopaminergic therapy, further research is needed to better understand these possible disparities.

Our finding that all nonmotor symptoms were negatively correlated with HRQOL confirms prior studies demonstrating the importance of nonmotor symptoms on HRQOL in PD<sup>2,30,33,37</sup> and provides additional information on prevalence and effect of individual nonmotor symptoms. In this cohort of relatively earlier stage PwPD, sleep-related, gastrointestinal, and neuropsychiatric symptoms were highly prevalent. Lack of interest, sad mood, decreased concentration, falls, and anxiety had the most substantially negative associations with HRQOL and may be impactful targets for symptom management. Depression has several proven treatments in PD,<sup>38</sup> but additional evidence from randomized controlled trials is needed to inform guidelines for PD-related depression and anxiety. Of note, many of these symptoms are associated with more advanced disease and worse HRQOL in these individuals may be due to unmeasured factors. Falls have previously been identified as predictive of worse QOL<sup>7</sup> and have far-reaching effects on mobility and independence, but there is a dearth of research on effective interventions.

We found depressive symptoms to be an important correlate of HRQOL, emphasizing the importance of identifying and treating neuropsychiatric symptoms in PwPD. Sad mood was endorsed by more than half of patients on the nonmotor survey and more than one third of patients reported symptoms of likely depression on the GDS, similar to prior prevalence studies showing that depression affects 35% of patients with PD.<sup>39</sup> The strong association of depression and HRQOL confirms findings from prior studies,<sup>40</sup> but we also found novel evidence that depression interacts with motor symptoms to affect well-being. Further research is needed to determine whether individuals with depression are more affected by their motor symptoms due to differences in symptom reporting, mood components of the experience of medication “off” times, or differential treatment of patients with and without depression. This is important because clinicians may need to utilize more targeted questioning in patients experiencing depression or increase focus on mood aspects of dopaminergic fluctuations.

We found that decreased self-reported cognitive function had a significant but small effect on QOL. Previous examinations of the relationship of objectively measured cognition and HRQOL have been mixed,<sup>6,29,41</sup> but with indications that attention may be a particularly important factor.<sup>42</sup> Due to the online nature of this study, patients with dementia may have been less likely to participate and we may be underestimating these differences. In addition, there may be collinearity with disease duration that attenuated the magnitude of our coefficients. Those with more severe cognitive impairment who

**Table 4** Results From Univariate and Multivariate Stepwise Linear Regression With Economic Burden Variables and EQ-5D Index in a Subcohort of Participants With Additional Economic Data (n = 890), Adjusting for Confounding Variables (Not Listed in the Table) and Significant Candidate Variables From the Main Analysis

Predictor	Mean ± SD or n (%)	β (95% CI)			
		Univariate	p Value	Multivariate	p Value
<b>Type of diagnosing provider</b>			0.05	-	-
	<b>Primary care doctor</b>	Ref			
	<b>Neurologist</b>	-0.02 (-0.10, 0.06)			
	<b>Movement specialist</b>	-0.00 (-0.08, 0.07)			
	<b>Other</b>	-0.15 (-0.28, -0.02)			
<b>Living location</b>			0.27	-	-
	<b>Urban</b>	Ref			
	<b>Suburban</b>	-0.01 (-0.04, 0.02)			
	<b>Rural</b>	-0.04 (-0.08, 0.01)			
	<b>Not sure</b>				
<b>Insurance status</b>			0.04	-	-
	<b>None</b>	Ref			
	<b>Private</b>	0.12 (-0.4, 0.27)			
	<b>Medicare</b>	0.08 (-0.08, 0.24)			
	<b>Military</b>	0.13 (-0.04, 0.29)			
	<b>Prefer not to answer</b>				
<b>Employment status</b>			<0.0001	-	-
	<b>Full time</b>	Ref			
	<b>Part time</b>	-0.02 (-0.08, 0.04)			
	<b>Retired</b>	-0.05 (-0.09, -0.14)			
	<b>Unemployed</b>	-0.206 (-0.32, -0.19)			
	<b>Prefer not to answer</b>				
<b>Hours of daily care</b>			<0.0001		0.006
	<b>None</b>	Ref		Ref	
	<b>Up to 16 hours</b>	-0.18 (-0.21, -0.15)		-0.02 (-0.05, 0.00)	
	<b>Around the clock</b>	-0.48 (-0.60, -0.37)		-0.15 (-0.25, -0.05)	

- = p > 0.05; excluded from multivariate model.

did participate may have been selected for by the involvement of a care partner, which itself affects HRQOL. Our finding that motor symptoms affect patients with likely more severe cognitive impairment more severely also raises questions of how treatment noncompliance or decreased frustration tolerance may worsen the experience of motor function.

In our exploratory analysis of the effect of economic factors, hours of daily care were the most significant contributor to poor HRQOL even after adjusting for disease duration, cognitive status, and motor symptom severity. Loss of functional

independence may be an independent risk factor for HRQOL deterioration, which confirms findings from another cohort of late-stage PD.<sup>43</sup> Insurance status, urban or rural living environment, and type of diagnosing provider did not significantly correlate with HRQOL in the multivariate model in this cohort, but exhibited trends that warrant further study in more socioeconomically diverse cohorts.

This analysis illustrates the key contributors to and disparities in HRQOL in PD in a larger, more broadly inclusive cohort than has previously been studied. The fully online design and



digital promotion strategies enabled the inclusion of PwPD outside of academic centers who are traditionally underrepresented in research. The large sample size enabled us to perform a more granular analysis of the effects of motor and nonmotor symptoms. This study adds to the growing effort by regulatory bodies to focus more on “the voice of the patient” to capture the experience of disease and to inform future studies.<sup>44</sup>

Our study has several limitations. Our analysis was cross-sectional and therefore conclusions are restricted to one point in time. All of our measures are self-reported, including the physician diagnosis of PD. However, studies show high rates of concordance between patient self-report and clinically determined diagnoses of PD.<sup>45-47</sup> Although broadly inclusive compared with many clinic-based studies, our cohort may not be representative of all PwPD as participation was contingent on Internet access and the ability to navigate an online platform. Individuals with lower income, living in more rural geographical areas, or with more cognitive issues likely encountered more challenges in accessing this study. Furthermore, participants who completed the full HRQOL assessment were less likely to have advanced disease compared with those who did not complete it. We therefore may be overestimating overall HRQOL and underestimating symptoms present in more advanced disease or PD dementia. Despite digital promotion efforts, recruitment of individuals traditionally underrepresented in research remained challenging, as evidenced by the higher income level and White predominance of this cohort compared with the overall US population.<sup>48</sup> Given socioeconomic discrepancies in PD care, this may have led to overestimation of HRQOL in our study or a lack of generalizability of results.<sup>36,49,50</sup> Nonmotor findings were rated only by their presence and not their severity; in future studies, the incorporation of more nuanced nonmotor scales will be informative. The EQ index, although well validated in PD,<sup>17,18</sup> is not a disease-specific measure of HRQOL. Mobility and depression/anxiety each comprise 20% of the overall EQ index score, so our associations found between depression and MDS-UPDRS score and overall HRQOL may be driven by these subdomains. We did not adjust for multiple comparisons. However, if we did take a more conservative approach of performing a Bonferroni correction and using an adjusted *p* value of 0.005 for our main regression analysis, the results are unchanged except that moderate to severe cognitive impairment no longer meets the threshold for statistical significance.

HRQOL is an important guiding concept for clinical encounters, therapeutic trials, and cost-effectiveness analyses. Understanding determinants of HRQOL is an essential first step in targeting its improvement by informing clinical and research priorities.

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<b>Ethan G. Brown, MD</b>	Movement Disorders and Neuromodulation Center, Department of Neurology, Weill Institute for Neuroscience, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
<b>Li Zhang, PhD</b>	Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
<b>Caroline Tanner, MD, PhD</b>	Movement Disorders and Neuromodulation Center, Department of Neurology, Weill Institute for Neuroscience, University of California, San Francisco; Parkinson’s Disease Research Education and Clinical Center, San Francisco Veteran’s Affairs Health Care System, CA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

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