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## **Non-motor vs motor symptoms: how much does each matter to health status in Parkinson's disease?**

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**ABSTRACT**

Evidence suggest that both motor and non-motor symptoms contribute to health status (HS) in Parkinson's disease (PD). Less clear is how much change in HS can be expected if these clinical variables change. In addition, anxiety, separate from depression, has rarely been examined as a predictor of HS. We used hierarchical multiple regression analysis and standardized beta coefficients in a prevalent cohort of 462 patients with Parkinson's disease to explore the relative impact on health status (measured using the Parkinson's Disease Questionnaire) of 5 well-recognized symptom domains in Parkinson's disease: motor signs, depression, anxiety, cognition, and other nonmotor symptoms. In the health status scores, 19.6% of variance was explained by age, number of comorbidities, disease duration, and levodopa equivalent dose. Younger age predicted worse health status. A full regression model containing baseline variables and all 5 symptom domains explained 56% of the variance in health status. The standardized beta coefficient for depression was 2.1, 1.6, and 1.3 times that of motor signs, anxiety, and other nonmotor symptoms, respectively. Our findings provide a ranking order of clinical variables for their relative impact on health status in Parkinson's disease and show that depression has more than twice the impact of motor signs on health status. Anxiety and other nonmotor symptoms are also important separate determinants of poor health status in Parkinson's disease. Our results will help to guide the development of individual care and service planning for patients with Parkinson's disease.

**Keywords:** relative contribution, Parkinson's disease, health status, quality of life, non-motor symptoms, depression, anxiety

## INTRODUCTION

In Parkinson's disease (PD), the primary means of improving health status (HS) has been through the better management of motor symptoms, but there is now evidence that non-motor symptoms also contribute to HS.<sup>1-7</sup> What remains less clear is the *relative* contribution of these clinical characteristics to HS; that is, what relative change can be expected to occur in HS when these factors change. This information is important in optimizing an individual patient's management, in understanding how changes in these factors influences the HS of a population of PD patients, and in facilitating decision-making regarding health resources in the management of PD.

Previous research has often been limited by sample size and inclusion of a limited number of possible predictors of HS making interpretation difficult. The relationship between depression and HS has been repeatedly demonstrated, but the role of anxiety, separate from depression, is not yet clearly understood. Also, physical co-morbidity has largely been ignored.<sup>8</sup> The current availability of several validated clinical measures<sup>9</sup> means that examination of the role of the broader range of non-motor symptoms (NMS) is now possible. Our study used validated measures in a large sample to systematically assess which clinical factors contribute to HS.

Our unique aim was to quantify the relative change in HS associated with change in the clinical variables. This extends previous studies by ranking the order of the motor and non-motor variables, and relatively quantifying their impact on HS. Based on existing literature,<sup>3, 6, 8, 10</sup> we hypothesized that motor symptom severity, depression, anxiety, cognition and non-motor symptoms would all contribute to HS, that mood and non-motor symptoms would be the strongest predictors of HS and changes in mood would have a larger effect on change in HS than changes in the other clinical variables. The term HS will be used to refer to impact on health.<sup>11</sup>

## **METHODS**

Patients with PD were recruited consecutively via neurology and care of the elderly clinics in the UK as part of a prospective study of mood (PROMS-PD).<sup>12</sup> Patients with a diagnosis of idiopathic PD according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria were eligible for inclusion. Patients with another neurological diagnosis inconsistent with a clinical diagnosis of idiopathic PD, severe hearing or visual loss or communication difficulties that would interfere with assessments were excluded. Cognitive impairment was not a specific exclusion criterion. After providing consent, all patients were assessed in their homes. The study was assessed and approved by the South East NHS Research Ethics Committee (Ref. 07/MRE01/9).

### **Assessments**

Assessments used standard published measures developed for or validated for use in PD. Information was collected from the patient and/or informant on clinical history and socio-demographics. Levo-dopa equivalent daily dose (LEDD) was calculated using conversion factors described previously.<sup>13</sup> Stage of disease was determined using the Hoehn and Yahr scale (H&Y).<sup>14</sup> Number of co-morbid physical conditions was assessed using the Physical Health measure from the Duke Older Americans Resources and Services assessment.<sup>15</sup> Motor symptoms were assessed using part III of the Unified Parkinson's Disease Rating Scale (UPDRS).<sup>16</sup> Patients were rated 'on' where possible for practical reasons. The Addenbrooke's Cognitive Exam-Revised (ACE-R)<sup>17</sup>, validated for use in PD, was used to assess cognition, with a total score of less than 84 indicating significant cognitive impairment.<sup>18</sup> The Hospital Anxiety and Depression Scale (HADS),<sup>19</sup> validated for use in PD,<sup>20</sup> was used to assess depression and anxiety symptoms. A subscale score greater than 10 indicates clinically significant depressive or anxiety symptoms while a score of 8-10 indicates possible

symptoms. We used the Non-Motor Symptom Scale (NMSS), developed and validated for use in patients with PD,<sup>9</sup> as a global measure of overall non-motor symptomatology based on severity and impact. To avoid overlap of the NMSS score with mood and cognition measures, we calculated a score for other NMS (ONMS) by excluding mood and cognition items from the NMSS (questions 7-12 and 16-18). HS was assessed using the Parkinson's Disease Questionnaire (PDQ-8), developed and validated in patients with PD and commonly used in both research and clinical practice.<sup>21-23</sup> It generates a single index score and produces results comparable to those gained from the larger PDQ-39.

### **Statistics and Analysis**

Demographic and disease-related characteristics were summarised with descriptive statistics and independent sample t-tests were used for comparison between groups. Clinical and demographic factors likely to impact HS (gender, age, disease duration, living alone, LEDD and number of physical comorbidities) were entered as independent variables into a baseline regression model using PDQ-8 as the dependent variable. Next, each of five symptom domains [motor symptom severity (UPDRS-III), depression (HADS-D), anxiety (HADS-A), cognition (ACE-R) and other non-motor symptoms (ONMS)] was added individually to the baseline model to assess their potential impact on HS. All symptom domains were measured on continuous scales. The Kolmogorov–Smirnov test showed that not all data were normally distributed, so Spearman's correlations were used to test for multicollinearity. All variables shown to be associated with HS in their own models were then entered together into a full regression model. The unique variance explained by each variable was determined by subtracting the variable in question from the full model. The relative impact of each symptom domain on HS was determined by using standardised regression coefficients. These coefficients were standardised to measure the impact on HS of minimally important change (MIC) on the measurement tools (where known).

## RESULTS

462 patients completed all assessments and were included in the analysis. Their characteristics are shown in Table 1. Possible and definite depression were present in 21.2% and 11.9% respectively, and these patients combined had significantly worse HS than those who were not depressed. Almost one-quarter (23.6%) of patients were on an anti-depressant at time of assessment.

A baseline regression model accounted for 19.6% of variance in PDQ-8 scores with worse HS predicted by a younger age, greater number of physical co-morbidities, living alone, longer disease duration and higher LEDD.

Each symptom domain contributed a significant amount of variance when entered independently after the baseline measures: depression (26.7% additional variance), anxiety (19.0%), non-mood and non-cognitive NMS (17.7%), motor symptom severity (9.0%) and cognition (2.5%). As each symptom domain significantly predicted HS in their individual regression models and there was no evidence of multicollinearity (all intercorrelations less than 0.6)<sup>24</sup> all planned variables were included in the full regression model.

The full model (Table 2) explained 56.2% of the variance in HS, an increase of 36.6% from the baseline model. The unique variance explained by each variable is shown in Table 3; depression explained the largest portion of variance, and more than ONMS, anxiety and motor state. The unique variance contributions obtained from the full model were smaller than those obtained from the individual regression models owing to the fact that domain scores were positively correlated. In the final model (adjusting for other domain effects), cognition was no

longer significantly associated with HS but the effects of the other four domains remained significant (Table 2).

The adjusted standardized beta coefficient (Table 2) obtained from the full model for HADS-D was 2.1, 1.6 and 1.3 times that of UPDRS III, HADS-A and ONMS respectively.

## **DISCUSSION**

The strengths of our study lie in its large sample, use of validated measures and use of an a priori specified hierarchical regression approach according to suggested best practice methods.<sup>24</sup> Analysis is based on predetermined hypotheses and is less likely to generate spurious results than automated variable selection methods. Although the removal of the mood and cognition components of the total NMSS means that our measure of “other NMS” is not a truly validated scale, the step was necessary to minimize overlap between the different measures and is analogous to motor studies using subsections of the UPDRS. We used the concept of MIC to interpret our data in a clinically relevant way. There is growing consensus regarding the clinically important effect size, and we used a half standard deviation, as suggested by Sloan et al.<sup>25</sup>

Our study has demonstrated the degree to which symptom domains in PD contribute to HS and provide a unique relative ranking of common domains affecting HS. We quantified this by showing that depression has more than twice the impact on HS than motor state and 1.6 times the impact of anxiety, that is, a half SD of change in depression (measured by HADSD) would lead to 2.1 times the impact on HS, compared with a half SD of change of motor state (measured by “on” UPDRS-III). These data can be clinically interpreted for UPDRS-III and HADS. The minimal change in UPDRS-III considered clinically important ranges from 2.3 to 5 points,<sup>26,27</sup> so the value for 0.5 SD of change in our data (5.8 points) would be considered

clinically meaningful. In terms of absolute numbers, available data on minimally important changes for HADS-D and HADS-A are sparse. In a population of patients with pulmonary disease, the minimal important difference on the HADS was found to be 1.5 points.<sup>28</sup> Therapeutic trials of antidepressants have reported differences in mean HADS scores ranging from 2.6 to 4.1 points.<sup>29</sup> Specifically in PD, mean differences of 1.7–2.7 points on the HADS were also considered meaningful.<sup>30</sup> Therefore, the change of 0.5 SD for HADS in our model (1.8–2.25 points) would be comparable to these. The degree of change in PDQ-8 affected by the magnitude of change in the independent variables confirmed that depression has greater than twice the impact of motor score and 1.6 times the impact of anxiety, but to our knowledge, no data are available on the minimal clinically important change for the NMSS or ACE-R to permit clinical interpretation for other NMSS or cognition. Given the cross-sectional nature of the study, our data and interpretations are offered as preliminary to raise awareness of this concept. Further studies are required before they can be used for clinical management or planning of patient care.

Our results extend the study by Schrag et al,<sup>6</sup> who used a different set of independent variables in a smaller cohort of 92 PD patients. They found depression (Beck Depression Inventory (BDI) was most predictive of HS, followed by disability (Schwab and England scale), postural instability (UPDRS-III subscore), and cognition (Folstein Mini-Mental State Examination). Two other studies, both using automated variable selection methods, are noteworthy for their large sample sizes. Qin et al<sup>31</sup> studied 391 mild–moderate PD patients in the “off” state and, using a variety of scales, found that depression, sleep disorders, and fatigue were significant predictors of HS (SF-36), whereas motor severity, disease stage, and LEDD did not make an independent contribution. The Global PD Survey Steering Committee<sup>32</sup> studied 902 PD patients and found that depression, H&Y stage, and

medication were significant predictors of HS (PDQ- 39) and explained a total of 59.7% of variance in HS.

However, a more limited number of variables were assessed than in our study. Numerous smaller studies have reported a contribution to HS from depression,<sup>3–5,8,33–36</sup> anxiety,<sup>8,34,35</sup> axial motor impairment,<sup>8</sup> shuffling gait,<sup>35</sup> bradykinesia,<sup>8</sup> motor symptom severity,<sup>37</sup> difficulty turning in bed,<sup>35</sup> cognition,<sup>2,4,6</sup> LEDD,<sup>4,8,33</sup> duration of L-dopa treatment,<sup>4</sup> disability,<sup>33–35</sup> disease severity,<sup>5,36</sup> age,<sup>5</sup> clinical fluctuations,<sup>36,37</sup> comorbidities,<sup>8</sup> and sleep problems.<sup>3</sup> Although the contribution of depression to HS is a consistent finding, a relative ranking of symptoms in terms of quantitative impact on HS is difficult to interpret from these studies.

We found that anxiety is an independent predictor of HS. It also has greater impact on HS than motor severity. Rahman et al<sup>35</sup> reported greater effects of depression (BDI) than anxiety (Beck Anxiety Inventory). In contrast, Muslimovic et al<sup>8</sup> found that depression and anxiety were related to HS to a similar extent. In a group of Brazilian PD patients, Carod-Artal et al<sup>34</sup> determined that depression and anxiety were correlated with PDQ-39; however, anxiety (HADS-A) and depression (HADS-D) were alternately included in multiple regression, so no clear conclusion could be drawn about the relative impact of one versus the other on HS.

Although there is growing interest in the role of anxiety in PD, which is, if anything, more common than depression,<sup>38</sup> our new results suggest that it may have less impact on HS than depression. A previous study using the NMSS demonstrated that the total score was the largest single predictor of HS (PDQ-8);  $r = 0.709$ . However, the NMSS contains items relating to depression, anxiety, cognition, and other symptoms, and so it is unclear the extent to which the broad range of NMS was contributing to HS rather than these specific measures. Our use of a restricted NMS score, eliminating mood and cognition components, demonstrated that the full range of other NMS was still highly predictive of HS, emphasizing

the importance of symptoms such as gastrointestinal, urinary, sexual, and sleep disturbance (although their independent interpretation is not considered in this study).

When considered with other symptoms, cognitive function did not emerge as an important predictor of HS, similar to the results of Muslimovic et al.<sup>8</sup> Visser et al.<sup>39</sup> demonstrated that PD patients with cognitive dysfunction are at risk for deterioration in quality of life over time, although not all studies support an association.<sup>5</sup> Klepac et al.<sup>40</sup> concluded that some of the reported association may be mediated by depression, with an association between cognitive impairment and HS only in patients with lower depression scores; in patients with higher depression scores, HS was poor regardless of cognitive status.

Several other points from our study are noteworthy. Few previous studies have addressed the impact of comorbid health conditions on HS in PD,<sup>8,34,36</sup> despite that this age group can be expected to have numerous other health conditions that could potentially influence HS. We found that despite being an independent predictor of HS, number of physical comorbidities lost significance when all symptom domains were included in the regression model; some of the variance explained by other health conditions may have been captured by symptoms measured by the ONMS (eg, pain, sleep disturbance). We found younger age predicted worse HS, perhaps reflecting the greater demands and expectations of younger PD patients.

Our findings are consistent with Schrag et al.,<sup>41</sup> who showed that moderate–severe depression was present in a significantly higher proportion of patients in a young-onset (<50 years) group (40%) compared with an old-onset (>50 years) group (17%).

Our study has several limitations. First, our large sample was composed of patients seen in specialist clinics and may not extrapolate to community-based samples. Second, the effects of normal aging are difficult to separate from the effects of PD without age-matched controls.

Third, many factors may contribute to the complex concept of HS, and although we measured selected variables hypothesized to contribute, a significant proportion of variance in HS remains unexplained. Fourth, as we did not measure the severity of patients' motor "off"-state symptoms, we cannot comment on their impact. However, as most patients are in an "on" state most of the time, the severity of symptoms in this state is probably more useful as an overall indicator of daily motor performance. Finally, because of the cross-sectional design, we were unable to make inferences regarding causality.

In summary, our findings emphasize the importance of focusing outcomes in PD on multiple measures of HS. We demonstrate that depression has more than twice the impact of motor state on HS. Anxiety, separate from depression, is also important and merits individual attention. Other combined nonmotor symptoms influence HS, but individual contributions cannot be extrapolated from this study. Cognition alone appears to influence HS but becomes less influential when combined with other symptoms; reasons for this are unclear. Younger age predicts worse HS, suggesting a need for heightened awareness in this group. Physical comorbidities do not independently influence HS. Our results are preliminary, but they emphasize the potential importance of screening for and managing depression, anxiety, and nonmotor symptoms in PD patients, individually and collectively. With further research, particularly longitudinal studies of measurement of change following targeted intervention, greater importance and more health resources may need to be attached to the management of NMS to improve patient outcome.

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**Table 1 – Patient characteristics (N=462)**

<b>Variable</b>	<b>Mean (SD)</b>	<b>Range</b>
<b>Demographic and social characteristics</b>		
age (years)	67.5 (10.3)	32-94
gender (% male)	64.9	-
ethnicity (% white)	96.3	-
currently working (% full- or part-time)	13.4	-
living alone (%)	20.1	-
<b>Physical health</b>		
number of physical health conditions including PD	2.9 (1.7)	1-11
<b>PD history and treatment</b>		
age of PD onset (years)	60.6 (11.9)	13-92
duration of PD since diagnosis (years)	5.0 (8.0) <sup>†</sup>	0-39
LEDD (mg/day)	600.0 (720.0) <sup>†</sup>	0-7365*
<b>Clinical scales</b>		
UPDRS-III total score	25.9 (11.6)	4-78
Hoehn & Yahr stages I/II-III/IV-V (%)	12.6/81.4/5.9	-
Total NMSS score	48.0 (52.3) <sup>†</sup>	0-235
ONMS (NMSS minus mood & cognition)	37.3 (35.3) <sup>†</sup>	0-150
HADS-depression score	6.1 (3.6)	0-17
HADS-anxiety score	7.1 (4.5)	0-20
ACE-R total score	86.9 (10.3)	46-100
PDQ-8 score	29.5 (18.5)	0-100

<sup>†</sup>Interquartile range

LEDD – levodopa equivalent daily dose; UPDRS-Unified Parkinson's Disease Rating Scale;

NMSS – Non-motor Symptoms Scale; ONMS – other non-motor symptoms; HADS –

Hospital Anxiety and Depression Scale; ACE-R – Addenbrooke's Cognitive Examination-

Revised; PDQ – Parkinson's Disease Questionnaire

\*This very high score represents a patient on continuous subcutaneous apomorphine infusion.

**Table 2. Results of final multiple regression analysis of PDQ-8 scores (final model)**

<b>Independent variables</b>	<b>Standardised regression (beta) coefficients</b>	<b>P-value</b>	<b>Regression coefficients</b>	<b>95% CI</b>	<b>Adjusted R<sup>2</sup>‡</b>
Gender	0.006	0.857	0.073	-0.718 – 0.864	
Age	-0.141	< 0.001*	-0.081	-0.124 – -0.039	
Living alone	0.047	0.144	0.684	-0.235 – 1.604	
No. of physical of health conditions	0.055	0.108	0.194	-0.043 – 0.431	
Duration of PD (yrs)	0.096	0.009*	0.095	0.024 – 0.167	
LEDD	0.074	0.039*	0.001	0.000 – 0.001	
ACE-R	-0.043	0.224	-0.025	-0.064 – 0.015	
UPDRS-III	0.148	< 0.001*	0.076	0.039 – 0.113	
HADS-A	0.196	< 0.001*	0.259	0.152 – 0.366	
NMSS (minus mood & cognition)	0.232	< 0.001*	0.053	0.036 – 0.069	
HADS-D	0.308	< 0.001*	0.503	0.373 – 0.633	
					0.562 (p<0.001)*

\*statistically significant results

‡ Adjusted R<sup>2</sup> = estimated proportion of the variance of PDQ-8 explained by the model including all listed independent variables.

**Table 3. Results of subtraction from full regression to determine unique variance portion of each variable.**

<b>Independent variables</b>	<b>Full model adjusted R<sup>2</sup></b>	<b>Adjusted R<sup>2</sup> with variable removed</b>	<b>Unique % variance explained by variable</b>
Depression	0.573	0.517	5.6%
NMSS*	0.573	0.536	3.7%
Anxiety	0.573	0.551	2.2%
UPDRS	0.573	0.560	1.3%
ACE-R	0.573	0.571	0.2%

\* NMSS minus mood and cognition components