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Non-motor symptoms burden, mood, and gait problems are the most significant factors contributing to a poor quality of life in non-demented Parkinson's disease patients: Results from the COPPADIS Study Cohort

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Abbreviations: ADLS, Schwab & England Activities of Daily Living Scale; BDI,, Beck Depression Inventory-II; EUROHIS-QOL8, European Health Interview Survey-Quality of Life 8 Item-Index; FOG, freezing of gait; FOGQ, freezing of gait Questionnaire; GQoL, Global quality of life; HRQoL, health-related quality of life; H&Y, Hoenh & Yahr; NMS, non-motor symptoms; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index; PDSS, Parkinson's Disease Sleep Scale; QoL, Quality of life; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; VAFS, Visual Analog Fatigue Scale; VAS-Pain, Visual Analog Scale-Pain

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ABSTRACT

Objective: To identify factors related to a poor health-related and global quality of life (QoL) in a cohort of non-demented Parkinson's disease (PD) patients and compare to a control group.
Methods: The data correspond to the baseline evaluation of the COPPADIS-2015 Study, an observational, 5-year follow-up, multicenter, evaluation study. Three instruments were used to assess QoL: (1) the 39-item Parkinson's disease Questionnaire (PDQ-39), (2) a subjective rating of global QoL (PQ-10), and (3) the EUROHIS-QOL 8-item index (EUROHIS-QOL8). Multiple linear regression methods were used to evaluate the direct impact of different variables on these QoL measures.
Results: QoL was worse in PD patients (n = 692; 62.6 ± 8.9 years old, 60.3% males) than controls (n = 206; 61 ± 8.3 years old, 49.5% males): PDQ-39, 17.1 ± 13.5 vs 4.4 ± 6.3 ($p < 0.0001$); PQ-10, 7.3 ± 1.6 vs 8.1 ± 1.2 ($p < 0.0001$); EUROHIS-QOL8, 3.8 ± 0.6 vs 4.2 ± 0.5 ($p < 0.0001$). A high correlation was observed between PDQ-39 and Non-Motor Symptoms Scale (NMSS) ($r = 0.72$; $p < 0.0001$), and PDQ-39 and Beck Depression Inventory-II (BDI-II) ($r = 0.65$; $p < 0.0001$). For health-related QoL (PDQ-39), non-motor symptoms burden (NMSS), mood (BDI-II), and gait problems (Freezing Of Gait Questionnaire [FOGQ]) provided the highest contribution to the model ($\beta = 0.32$, 0.28, and 0.27, respectively; $p < 0.0001$); whereas mood and gait problems contributed the most to global QoL (PQ-10, $\beta = -0.46$ and -0.21, respectively; EUROHIS-QOL8, $\beta = -0.44$ and -0.23, respectively).
Conclusions: QoL is worse in PD patients than in controls. Mood, non-motor symptoms burden, and gait problems seem to be the most relevant factors affecting health-related and global perceived QoL in non-demented PD patients.

1. Introduction

Parkinson's disease (PD) is characterized by motor and non-motor manifestations. In contrast to motor dysfunction, non-motor symptoms (NMS) remain frequently unreported unless specifically investigated [1]. However, their identification is important because NMS are frequent and negatively impact the quality of life (QoL) of PD patients [2,3]. Improving or keeping QoL is very important in chronic diseases, such as PD, for which a cure does not exist [4]. So, currently the aim of PD management is, as a whole, to improve QoL and autonomy of the patient for activities of daily living. To achieve this objective, it is necessary to know which factors are contributing to QoL, deterioration, and disability, in order to revert or neutralize those susceptible of intervention [5]. Different studies have analyzed factors contributing to a poor QoL in PD patients [2–16]. However, limitations in some studies about this topic are the sample size, differences between scales used for assessing QoL, different types of QoL assessed, development in only one center, and/or the lack of a global evaluation including different aspects that could impact on QoL. For example, mood is frequently included in studies assessing QoL in PD, but an important problem like freezing of gait (FOG) is not.

The aim of the present study is to identify factors that influence health-related QoL (HRQoL) and global QoL (GQoL) in a population of PD patients from the COPPADIS-2015 Study Cohort, a comprehensive observational, 5-year follow-up, nationwide, multicenter study [17].

2. Methods

Non-demented PD patients and controls (subjects without PD and any other disabling concomitant neurological or non neurological disease) from the COPPADIS-2015 Study Cohort [17] were included in this study. The recruitment period was from January 1, 2016 to October 31, 2017. The data correspond to the baseline evaluation of the cited study (cross-sectional study). All patients were diagnosed according to UK PD Brain Bank criteria [18]. Exclusion criteria were: parkinsonism other than PD, dementia according to Movement Disorder Society criteria (Mini Mental State Examination [MMSE] < 26), age < 18 or > 75 years, inability to read or understand the questionnaires, to be receiving any advanced therapy (continuous infusion of levodopa or apomorphine, and/or with deep brain stimulation), and presence of comorbidity, sequelae, or any disorder that could interfere with the assessment [17]. The study was approved by the ethics committee at each participating institution. All participants signed an informed consent form.

Information on sociodemographic aspects, factors related to PD, comorbidity, and treatment was collected. Patient baseline evaluation included motor assessment (Hoenh & Yahr [H&Y], Unified Parkinson's Disease Rating Scale [UPDRS] part III and part IV, Freezing of Gait Questionnaire [FOGQ]), non-motor symptoms (Non-Motor Symptoms Scale [NMSS], Parkinson's Disease Sleep Scale [PDSS], Visual Analog Scale-Pain [VAS-Pain], Visual Analog Fatigue Scale [VAFS]), cognition (MMSE, Parkinson's Disease Cognitive Rating Scale [PD-CRS], completing a simple 16-piece puzzle), mood and neuropsychiatric symptoms (Beck Depression Inventory-II [BDI-II], Neuropsychiatric Inventory [NPI], Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale [QUIP-RS]), and disability (Schwab & England Activities of Daily Living Scale [ADLS]) [17]. In patients with motor fluctuations, the motor assessment was made during the OFF state (without medication in the last 12 h) and during the ON state. While in patients without motor fluctuations, the assessment was only performed without medication. Three different instruments were used to assess QoL: (1) the 39-item Parkinson's disease Questionnaire (PDQ-39) [19], (2) a rating of global perceived QoL (PQ-10) on a scale from 0 (worst) to 10 (best) [20], and (3) the EUROHIS-QOL 8-item index (EUROHIS-QOL8) [21]. The PDQ-39 is a PD-specific questionnaire that assesses the patients' HRQoL. There are 39 items grouped into 8 domains: (1) Mobility (items 1 to 10); (2) Activities of daily living (items 11 to 16); (3) Emotional well-being (items 17 to 22); (4) Stigma (items 23 to 26); (5) Social support (items 27 to 29); (6) Cognition (items 30 to 33); (7) Communication (items 34 to 36); (8) Pain and discomfort (items 37 to 39). For each item, the score may range from 0 (never) to 4 (always). The symptoms refer to the 4 weeks prior to assessment. Domain total scores are expressed as a percentage of the corresponding maximum possible score and a Summary Index is obtained as average of the domain scores. The EUROHIS-QOL8 is an 8-item GQoL questionnaire (quality of life, health status, energy, autonomy for activities

of daily living, self-esteem, social relationships, economic capacity, and habitat) derived from the WHOQOL-BREF. For each item, the score ranges from 0 (not at all) to 5 (completely). The total score is expressed as the mean of the individual scores. A higher score indicates a better QoL.

The same evaluation as for the patients, except for the motor assessment, was performed in control subjects.

2.1. Statistical analysis

Data were analyzed using SPSS 20.0 for Windows. For PDQ-39, PQ-10 and EUROHIS-QOL8, mean values were compared by the Mann-Whitney test (the Kolmogorov–Smirnov test showed that data were not normally distributed), and Spearman rank correlation coefficients were calculated to assess the direction and magnitude of association between variables. Correlations were considered weak for coefficient values ≤ 0.29, moderate for values between 0.30 and 0.59, and strong for values ≥ 0.60. Stepwise multiple regression analysis was used to determine the factors that best accounted for variance in HRQoL (PDQ-39) and GQoL (PQ-10 and EUROHIS-QOL8) scores. Collinearity was excluded among the variables that entered the regression model. Due to the number of different comparisons, statistical significance was only accepted at $p < 0.0001$.

3. Results

A total of 694 PD patients and 207 controls were recruited and considered valid after a monitoring process in the COPPADIS-2015 Study (Fig. 1 – Supplementary Material). Of them, 2 patients and 1 control were excluded due to lack of key data for the analysis, so finally 692 PD patients (62.6 ± 8.9 years old, 60.3% males) and 206 controls (61 ± 8.3 years old, 49.5% males) were included for analysis. Data about sociodemographic variables, comorbid conditions, and therapies in PD patients and in controls are shown in Table 1 – Supplementary Material. Data about motor and non-motor evaluations in PD and/or in controls are shown in Table 2 – Supplementary Material. The mean disease duration from onset was 5.5 ± 4.4 years, more than 90% of the patients were on stage I or II of H&Y. More than a quarter of patients presented motor complications and a majority of them were taking levodopa, as the mean levodopa equivalent daily dose of 555.8 ± 411.3 mg. The score of all the scales of the non-motor evaluation was significantly better in the controls with respect to the patients, so non-motor burden was significantly higher in PD patients.

QoL was worse in PD patients than in controls: PDQ-39, 17.1 ± 13.5 vs 4.4 ± 6.3 ($p < 0.0001$); PQ-10, 7.3 ± 1.6 vs 8.1 ± 1.2 ($p < 0.0001$); EUROHIS-QOL8, 3.8 ± 0.6 vs 4.2 ± 0.5 ($p < 0.0001$). With regards to the domains of PDQ-39 and the questions of EUROHIS-QOL8, scores reflected a worse QoL in PD patients that in controls (Table 1). For PD patients, the highest score was for the PDQ-39-domain 8 (pain and discomfort) and the lowest score was for the PDQ-39-domain 5 (social support); however, for controls, the PDQ-39-domain 3 (emotional well-being) and the PDQ-39-domain 4 (stigma) were the highest and the lowest scores obtained, respectively. In relation to the GQoL, the impression on the state of health was the worst domain of EUROHIS-QOL8 in both patients and controls. Strong correlation was observed between PQ-10 and EUROHIS-QOL8, both scales for provide GQoL ($r = 0.68$ for all population, patients plus controls [$p < 0.0001$]; $r = 0.67$ for PD patients [$p < 0.0001$]). Moreover, the correlation in PD patients between PDQ-39 and the health status domain of the EUROHIS-QOL8 was moderate ($r = -0.49$).

In PD patients, QoL was worse in women than in men (PDQ-39, 18.9 ± 13.7 vs 16 ± 13.3 [$p = 0.007$]; PQ-10, 7.2 ± 1.6 vs 7.4 ± 1.5 [$p = 0.90$]; EUROHIS-QOL8, 29.8 ± 4.6 vs 30.7 ± 4.3 [$p = 0.012$]); in patients with motor fluctuations (PDQ-39, 24.2 ± 14.8 vs 13.6 ± 11.3 [$p < 0.0001$]; PQ-10, 6.9 ± 1.6 vs 7.5 ± 1.5 [$p < 0.0001$]; EUROHIS-QOL8, 29.1 ± 4.4 vs 30.9 ± 4.3 [$p < 0.0001$]); and patients with dyskinesia (PDQ-39, 25.6 ± 15.4 vs 15.3 ± 12.3 [$p < 0.0001$]; PQ-10, 6.7 ± 1.6 vs 7.4 ± 1.5 [$p < 0.0001$]; EUROHIS-QOL8, 28.5 ± 4.5 vs 30.7 ± 4.3 [$p < 0.0001$]) and falls (PDQ-39, 31 ± 15 vs 15 ± 11.9 [$p < 0.0001$]; PQ-10, 6.4 ± 1.7 vs 7.4 ± 1.5 [$p < 0.0001$]; EUROHIS-QOL8, 26.9 ± 4.3 vs 30.8 ± 4.2 [$p < 0.0001$]).

HRQoL (PDQ-39) was better in PD patients with tremoric phenotypes compared to postural instability gait difficulty (PIGD) and indeterminate phenotypes [17] (14.6 ± 12.5 vs 19.4 ± 13.7 vs 18.9 ± 14.7, respectively [$p < 0.0001$]); whereas GQoL (PQ-10) was worse in PIGD patients compared to tremoric and indeterminate phenotypes (7 ± 1.6 vs 7.5 ± 1.5 vs 7.5 ± 1.5, respectively [$p = 0.003$]).

A high correlation was observed between PDQ-39 and NMSS ($r = 0.71$; $p < 0.0001$), and PDQ-39 and BDI-II ($r = 0.65$; $p < 0.0001$). Table 2 shows correlations between PDQ-39, PQ-10, and EUROHIS-QOL8 and other variables. With regards to NMS burden [22] and depressive symptoms (DSM-IV criteria and Judd criteria [17]), the greater severity of symptoms, the poorer QoL was observed (Fig. 1). Considering the different domains of the NMSS, mood/apathy ($r = 0.65$; $p < 0.0001$) and sleep/fatigue ($r = 0.59$; $p < 0.0001$) presented the strongest correlation to HRQoL whereas sexual dysfunction ($r = 0.32$; $p < 0.0001$) the weakest. In the case of GQoL, the strongest correlation was to mood/apathy (PQ-10, $r = -0.42$ [$p < 0.0001$]; EUROHIS-QOL8, $r = -0.53$ [$p < 0.0001$]) and sleep/fatigue (PQ-10, $r = -0.37$ [$p < 0.0001$]; EUROHIS-QOL8, $r = -0.47$ [$p < 0.0001$]) whereas to gastrointestinal symptoms (PQ-10, $r = -0.15$ [$p < 0.0001$]; EUROHIS-QOL8, $r = -0.21$ [$p < 0.0001$]) the weakest.

For HRQoL, non-motor symptoms burden (NMSS), mood (BDI-II), and gait problems (FOGQ) provided the highest contribution to the model ($\beta = 0.32$, 0.28 and 0.27, respectively; $p < 0.0001$; adjusted R-squared 0.66), whereas mood and gait problems for GQoL (PQ-10, $\beta = -0.46$ and -0.21, respectively [adjusted R-squared 0.31]; EUROHIS-QOL8, $\beta = -0.44$ and -0.23, respectively [adjusted R-squared 0.47]) (Table 3). When the analysis was performed only in the subgroup of patients with a disease duration ≤5 years (n = 399; 62 ± 9 years old, 58.4% males; mean disease duration 2.7 ± 1.5 years), similar results were obtained. For PDQ-39, NMSS ($\beta = 0.38$),

Table 1
Health-related (PDQ-39SI) and global perceived (PQ-10 and EUROHIS-QOL8) quality of life in PD patients (n = 692) vs controls (n = 206).

	Patients	Controls
PDQ-39SI	**17.1 ± 13.5**	**4.4 ± 6.3**[a]
Mobility	16.6 ± 19.2	3 ± 9
Activities of daily living	18 ± 18.6	0.7 ± 2.6
Emotional well-being	21.5 ± 20	10.6 ± 16.2
Stigma	13.5 ± 19.5	0.4 ± 2.2
Social support	8.2 ± 16.5	3.2 ± 9.6
Cognition	19.3 ± 17.9	7.4 ± 12.1
Communication	10.2 ± 15.3	0.9 ± 2.8
Pain and discomfort	26.4 ± 22.8	9.4 ± 16.4
PQ-10	**7.3 ± 1.6**	**8.1 ± 1.2**
EUROHIS-QOL8	**3.8 ± 0.6**	**4.2 ± 0.5**
Quality of life	3.8 ± 0.7	4.2 ± 0.6
Health status	3.2 ± 0.9	4 ± 0.7
Energy	3.8 ± 0.8	4.2 ± 0.7
Autonomy for activities of daily Living	3.6 ± 0.9	4.3 ± 0.7
Self-esteem	3.8 ± 0.8	4.2 ± 0.7
Social relationships	4.1 ± 0.7	4.4 ± 0.6
Economic capacity	3.9 ± 0.8	4.2 ± 0.7
Habitat	4.2 ± 0.7	4.4 ± 0.6

EUROHIS-QOL8, EUROHIS-QOL 8-item index; PDQ-39SI, 39-item Parkinson's disease Quality of Life Questionnaire Summary Index score; PQ-10, Perceived Quality of Life.

[a] For PDQ-39, n = 168 in control group. All comparisons between patients and controls were significant at a $p < 0.0001$ level (Mann-Whitney-Wilcoxon test).

Table 2
Correlations between PDQ-39SI, PQ-10 and EUROHIS-QOL8, and other variables about motor and non-motor symptoms in PD patients.

	PDQ-39SI	PQ-10	EUROHIS-QOL8
Age	−0.04[a]	0.02[a]	0.03[a]
Years of disease from onset	0.23	−0.10[b]	−0.10[b]
Eq. daily dose of L-dopa (mg)	0.25	−0.12[c]	−0.13[c]
Hoehn & Yahr	0.35	−0.14	−0.22
UPDRS-III	0.43	−0.17	−0.26
UPDRS-IV	0.48	−0.31	−0.31
MMSE	−0.13	0.14	0.13[c]
PD-CRS	−0.16	0.16	0.22
NMSS	0.71	−0.41	−0.53
BDI-II	0.65	−0.48	−0.60
NPI	0.50	−0.36	−0.45
QUIP-RS	0.24	−0.01[a]	−0.12[c]
PDSS	−0.51	0.32	0.39
VAS-PAIN	0.37	−0.25	−0.32
VASF – physical	0.49	−0.37	−0.44
VASF – mental	0.47	−0.33	−0.39
FOGQ	0.57	−0.32	−0.39
ADLS	−0.56	0.33	0.45

Spearman's rank correlation coefficient, all significant at a $p < 0.0001$ level, except: [a] N·S.: not significant, [b] < 0.05–0.01; [c] < 0.01–0.001; [d] < 0.00.1.
ADLS, Schwab & England Activities of Daily Living Scale; BDI-II, Beck Depression Inventory-II; FOGQ, Freezing Of Gait Questionnaire, NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index; PDSS, Parkinson's Disease Sleep Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; VAFS, Visual Analog Fatigue Scale; VAS-Pain, Visual Analog Scale -Pain.

FOGQ ($\beta = 0.32$) and BDI-II ($\beta = 0.25$) provided the highest contribution to the model ($p < 0.0001$; adjusted R-squared 0.61) along with age (β = -0.11; $p = 0.001$); for PQ-10, BDI-II, physical fatigue (VASF) and FOGQ provided the highest contribution ($\beta = -0.29$, -0.19 and -0.18, respectively [adjusted R-squared 0.30] along with cognition (PD-CRS, $\beta = 0.15$; $p = 0.002$); and for EUROHIS-QOL8, BDI-II, FOGQ and age provided the highest contribution (β = -0.38, -0.21 and 0.17, respectively [adjusted R-squared 0.43] along with NMSS (β = -0.16; $p = 0.004$) and cognition ($\beta = 0.15$; $p = 0.001$).

Finally, and after the relationship observed between gait problems and QoL, we analyzed QoL in patients classified regarding to FOGQ-item 3 (FOG Score) as patients with FOG (n = 239; 34.7%) vs without FOG (freezing of gait) (n = 450; 65.3%). QoL was significantly worse in PD patients with FOG: PDQ-39, 25.7 ± 15.6 vs 12.7 ± 9.6 ($p < 0.0001$); PQ-10, 6.7 ± 1.7 vs 7.6 ± 1.4 ($p < 0.0001$); EUROHIS-QOL8, 3.5 ± 0.6 vs 3.9 ± 0.5 ($p < 0.0001$). Similar results were obtained when the analysis was performed in the subgroup of patients with a disease duration ≤5 years (23.8% with FOG): PDQ-39, 24.1 ± 14.5 vs 11.8 ± 8.9 ($p < 0.0001$); PQ-10, 6.8 ± 1.8 vs 7.6 ± 1.4 ($p < 0.0001$); EUROHIS-QOL8, 3.5 ± 0.6 vs 3.9 ± 0.5 ($p < 0.0001$). In all multiple regression analysis (PDQ-39, PQ-10 and EUROHIS-QOL8 as dependent variables), when FOGQ was changed to FOG score, FOG was a significant factor related to a worse QoL ($p < 0.0001$) in both populations, the global cohort (n = 692) and the subgroup of patients with disease duration ≤ 5 years (n = 399), except for PQ-10 in the subgroup with ≤5 years of disease duration ($p = 0.051$).

4. Discussion

The present study demonstrates that in non-demented PD patients the most relevant factors contributing to a worse QoL are NMS burden, mood, and gait problems. These factors had the strongest impact on both specific HRQoL (PDQ-39) and GQoL (EUROHIS-QOL8). Considered together, the contribution of NMS burden (NMSS), plus mood (BDI-II), plus gait problems (FOGQ) to HRQoL and GQoL was significant.

The clinical characteristics and assessment results of our PD sample were similar to those of comprehensive previous studies [2–8]. Our

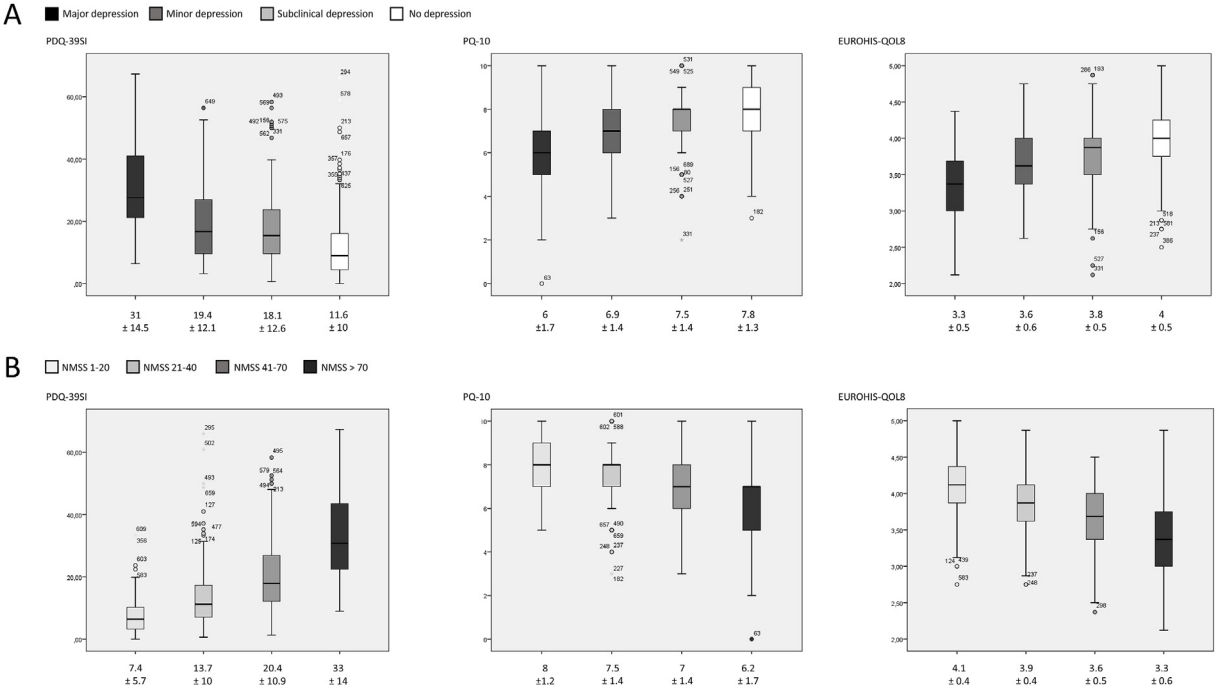

Fig. 1. Health-related (PDQ-39SI) and global perceived quality of life (PQ-10 and EUROHIS-QOL8) are represented in patients regarding to (A) depressive symptoms (major vs minor vs subclinical vs no depression) [17] and (B) NMS burden (mild [NMSS 1–20] vs moderate [NMSS 21–40] vs severe [NMSS 41–70] vs very severe [NMSS > 70]) [22]. NMSS, Non-Motor Symptoms Scale. PDQ-39SI; 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index. All analysis were significant at a $p < 0.0001$ level.

Table 3
Multiple regression models for PDQ-39SI, PQ-10 and EUROHIS-QOL8 as dependent variables.

	Adjusted	B standardized coefficient	CI 95%	*P* value
	R-squared			
Model for PDQ-39SI	0.66			
NMSS		0.32	0.09, 0.14	< 0.0001
BDI-II		0.28	0.42, 0.64	< 0.0001
FOGQ		0.27	0.63, 0.97	< 0.0001
PDSS		−0.12	−0.09, −0.04	< 0.0001
Model for PQ-10				
BDI-II	0.31	−0.46	−0.11, −0.08	< 0.0001
FOGQ		−0.21	−0.09, −0.04	< 0.0001
Model for EUROHIS-QOL8				
BDI-II	0.47	−0.44	−0.04, −0.03	< 0.0001
FOGQ		−0.23	−0.04, −0.02	< 0.0001
NMSS		−0.17	−0.00, −0.00	< 0.0001

Age, gender, disease duration, H&Y (OFF), UPDRS-III (OFF), UPDRS-IV, PD-CRS, NMSS, BDI-II, QUIP-RS, NPI, PDSS, VAS-PAIN, VASF-physical, VASF-mental and FOGQ were included initially in the model. The model included finally those variables with most significant impact ($p < 0.0001$) on dependent variable adjusted by age and gender.

BDI-II, Beck Depression Inventory-II; FOGQ, Freezing Of Gait Questionnaire, NMSS, Non-Motor Symptoms Scale; PDSS, Parkinson's Disease Sleep Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

observations indicate, as it is known, PD is not only a motor disorder, and PD patients suffer from different NMS even during the first steps of the disease [1]. In fact, 9 out 10 patients of our cohort were on H&Y stage I or II; however, cognitive impairment, pain, fatigue, depression, sleep problems, or impulsive behaviors were more frequent in PD patients than in controls. Previous studies have demonstrated that NMS burden assessed with the NMSS is higher in PD patients than in controls [6]; however, some symptoms are not detected if they are not explored properly. For example, although all patients included in the present study had a MMSE score ≥26, around 30% of them presented cognitive impairment when cognition was assessed using the PD-CRS. Moreover, the number of drugs including antidepressant agents, analgesics, and pills taken per day were higher in PD patients than in controls. As a whole, these data reflect the picture of PD, a complex disorder with many different symptoms causing disability and a poor QoL.

With regards to QoL, the results were similar to other studies which used the PDQ-39, as "pain and discomfort" was the most affected domain and "social support" was the least [2]. Interestingly, "health status" was the most affected domain in global GQoL not only in PD patients but also in controls, which may suggest a tendency to be more demanding by people in general with the perception of health status as condition factor of QoL. In a survey on 4,849 European adults, the item about health status was also the most affected after economic capacity [23]. Different factors have been reported to be related to a worse QoL in PD, such as older age [9], comorbidities [10], levodopa equivalent daily dose [10,11], duration of levodopa treatment [12], disability [8,11,13], disease severity [9,14], motor symptoms severity [15], bradykinesia [10], axial motor impairment [10], shuffling gait [13], difficulty turning in bed [13], clinical fluctuations [14,15], anxiety [14,15], depression [8], cognition [8,16], or sleep problems [16]. In our study, age was not related to QoL but other factors were, ranging from weak (disease duration, cognition, impulse behavior) to moderate correlations (motor stage, motor complications, neuropsychiatric symptoms, sleep problems, pain, fatigue, gait problems, disability). The comparison between different studies in any case is conditioned by differences in sample size, methodology used or characteristics of the samples (Table 3 – Supplementary Material). Two factors correlated strongly with HRQoL: NMS burden and mood. The contribution of depression to HRQoL in PD is a consistent finding in the literature, even in studies using different methodologies, which is one of the reasons why it is considered a determinant of QoL [4,8,16]. In our study, the perception of QoL was clearly related to mood status, being better in patients without depression and progressively worse in those with higher depression degree severity (subclinical depression, minor depression, and major depression). Previous studies have suggested that NMS burden could be an independent predictor of HRQoL [2,3,7,24], but the concomitant effect of mood assessed with an specific scale was frequently not taken into account [2,3]. Hinnell et al. [7] did show a direct negative impact of NMS on HRQoL (as assessed by the PDQ-8) after adjusting for mood. More recently, it was found that some NMS such as depressed mood, apathy, pain, and fatigue contributed to a worse QoL in the largest study related to HRQoL issues in PD [25]. Interestingly, in our study, both HRQoL and GQoL were progressively worse with regards to the grade of NMS burden: mild, moderate, severe, and very severe. This was observed previously by Chaudhuri et al. [22]. Regarding to the relationship between NMS and QoL and in line with other studies [2], mood/apathy and sleep/fatigue were the domains from the NMSS more related to both HRQoL and GQoL. Moreover, QoL was better in tremoric phenotype patients and men, as it had been reported before [26,27].

An important observation in the present study is the fact that gait problems are one of the complications that contribute more to both, HRQoL and GQoL. Previous studies demonstrated that freezing of gait (FOG) has a significant negative impact on HRQoL [28,29]. In our study, QoL was worse in PD patients who suffered falls. Also, total FOGQ score contributed independently of the effect of other covariates to PDQ-39 and EUROHIS-QOL8 scores. An important aspect is the fact that this is the largest study related to HRQoL and GQoL issues in PD (692 patients and 206 controls) in which an exhaustive motor and non-motor evaluation with more than 15 validated scales and multiple variables were analyzed [17]. Moore et al. [29] also used the FOGQ but the sample was 118 patients and they adjusted the FOGQ score only for UPDRS, H&Y, disease duration, age, and gender. Walton et al. [28] included 203 patients and only studied the effect of FOG on HRQoL but not on GQoL. Interestingly, in our study, FOGQ was a significant contributor to a worse QoL even in the subgroup of patients with no more than 5 years of disease duration, which suggests that gait disturbances is a relevant factor affecting QoL also in early PD and that it is important to consider this problem and to look for it in early PD patients. Specifically, FOG was frequent even in early PD patients and was associated to a worse QoL, being our results in line with a previous study [30]. Moreover, NMS burden and depressed mood contributed very significantly to QoL in our cohort. These results are in line with previous studies [2,3,7,8]. Considered together, NMS burden (NMSS), mood (BDI-II), gait problems (FOGQ), and sleep problems [PDSS]) explained about 65% and 45% of the variance of HRQoL and GQoL, respectively. This observation could be explained by the fact that QoL is a complex concept to which many factors other than health contribute,

but in any case, the results are similar to those of other studies [2,8]. GQoL is the general well-being of the individual and observes life satisfaction, including not only physical health but also other aspects such as self-esteem, autonomy or economic capacity. As we observe using the PQ-10 scale and the EUROHIS-QOL8 questionnaire, mood (BDI-II) influences GQoL perception because this one is a subjective impression according to the mood at the moment, and gait problems (FOGQ) influences too because something essential for having a good perception of GQoL is autonomy for activities of daily living and to have a good mobility is necessary. However, HRQoL is a concept only associated with a health state. The information contained in the eight PDQ-39 domains is about different aspects related to PD and this would explain that not only mood and gait problems but also other symptoms may influence the perception of the state of health. As it has been previously reported [20], the impact of mood on QoL seems to be higher for GQoL than HRQoL. When ADLS score was included in the model, results were similar with regards to NMS, mood, and FOGQ. Furthermore, although mood is included in NMSS (NMSS-domain (3), when mood was excluded from the NMS burden ([NMSS total score] – [NMSS-domain 3]), results were again similar. Finally, the low impact of cognition and neuropsychiatric symptoms could be explained due to the characteristics of the sample, with a relatively small proportion of elderly patients, without dementia, and with short disease duration as a whole.

The present study has some limitations. For some variables, the information was not collected in all cases. All scales or questionnaires used for assessing motor and NMS are validated except PQ-10. This is a very simple question about GQoL from 0 to 10 used in a previous study [20]. To use the PQ-10 takes very little time and provides information similar to the EUROHIS-QOL8 total score. Age and other characteristics were similar in both groups, PD patients and controls, except gender and education level, with about 10% more of females in control group and 10% more with primary education level in PD patients group. Our sample was not fully representative of the PD population due to inclusion and exclusion criteria (i.e., age limit, no dementia, no severe comorbidities, no second line therapies, etc.) and a bias toward early PD exists. Finally, this is a cross-sectional study, but the aim of the COPPADIS-2015 study [17] is to follow-up the cohort for 5 years and to analyze predictors of changes in QoL.

As conclusion, NMS burden, mood, and gait problems seem to be the most significant factors contributing to a poor QoL in non-demented PD patients. The methodology is consistent and the results are relevant. In daily clinical practice, it is necessary to ask about NMS, mood, and gait problems in patients with PD during their first years of evolution because through acting on these problems, we could improve their QoL.

Conflicts of interest

None.

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Authors' roles

Diego Santos-García, MD, PhD: conception, organization, and execution of the project; statistical analysis; writing of the first draft of the manuscript; recruitment and/or evaluation of participants.

De Deus Fonticoba T: review and critique; evaluation of participants.

Suárez Castro E: review and critique; evaluation of participants.

Borrué C: review and critique; recruitment and/or evaluation of participants.

Mata M: review and critique; recruitment and/or evaluation of participants.

Solano Vila B: review and critique; recruitment and/or evaluation of participants.

Cots Foraster A: review and critique; recruitment and/or evaluation of participants.

Álvarez Sauco M: review and critique; recruitment and/or evaluation of participants.

Rodríguez Pérez AB: review and critique; recruitment and/or evaluation of participants.

Vela L: review and critique; recruitment and evaluation of participants.

Macías Y: review and critique; evaluation of participants.

Escalante S: review and critique; recruitment and/or evaluation of participants.

Esteve P: review and critique; recruitment and/or evaluation of participants.

Reverté S: review and critique; recruitment and/or evaluation of participants.

Cubo E: review and critique; recruitment and/or evaluation of participants.

Casas E: review and critique; recruitment and/or evaluation of participants.

Arnaiz S: review and critique; recruitment and/or evaluation of participants.

Carrillo Padilla F: review and critique; recruitment and/or evaluation of participants.

Pueyo MP: review and critique; recruitment and/or evaluation of participants.

Mir P: review and critique; recruitment and/or evaluation of participants.

Martinez Martin P: review and critique; overall supervision.

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Appendix A. Supplementary data

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