RESEARCH ARTICLE

Impact of Apathy on Health-Related Quality of Life in Recently Diagnosed Parkinson's Disease: The ANIMO Study

Julián Benito-León, MD, PhD,[1,2,3]* Esther Cubo, MD, PhD,[4] and Carlos Coronell, MD, PhD,[5] on behalf of the ANIMO Study Group

[1]*Department of Neurology, University Hospital ''12 de Octubre'', Madrid, Spain*
[2]*Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Madrid, Spain*
[3]*Department of Medicine, Faculty of Medicine, Complutense University, Madrid, Spain*
[4]*Department of Neurology, Hospital ''General Yagüe,'' Burgos, Spain*
[5]*Medical Advising Department, Boehringer Ingelheim España, Barcelona, Spain*

ABSTRACT: The impact of apathy on health-related quality of life (HRQOL) in recently diagnosed Parkinson's disease (PD) has not been systematically investigated. The objective of this cross-sectional survey (ANIMO study) was to examine the contribution of apathy to HRQOL in a Spanish sample of recently diagnosed PD patients. PD patients, diagnosed within 2 years of inclusion, were recruited at 102 outpatient clinics in 82 communities throughout Spain. Apathy was quantified using the Lille Apathy Rating Scale and HRQOL with the EuroQol-5D questionnaire. A mean EuroQol-5D index score of 0.89 obtained from population references in Spain was used as the cutoff for this study. The relationship between apathy and the dichotomized EuroQol-5D index score (<0.89 [lower HRQOL] vs ≥0.89 [reference]) was examined using multiple logistic regression analysis, adjusting for sociodemographic and clinical variables. We consecutively recruited 557 patients (60.3% men) with a mean age of 68.8 ± 9.7 years. Apathy was diagnosed in 291 (52.2%) and was related to problems in each of the EuroQoL dimensions. Apathetic PD patients showed EuroQol-5D index scores significantly lower than those without apathy (0.64 vs 0.83). In an adjusted model, apathetic PD patients were 2.49 times more likely to have lower HRQOL than nonapathetic patients (odds ratio, 2.49; 95% confidence interval, 1.49–4.15, $P < 0.01$). Apathy is very common in those with recently diagnosed PD and is one of the major clinical determinants of HRQOL in this disease. It should be one of the primary concerns among clinicians who provide treatment to individuals affected by PD.

Key Words: apathy; Parkinson's disease; quality of life; EuroQol; Spain

Traditional medical models of impairment and disability provide an incomplete summary of disease burden.[1,2] Hence, in recent years, measures of health-related quality of life (HRQOL) are increasingly being incorporated into studies of a variety chronic conditions, including neurodegenerative disorders.[1–4] HRQOL involves those aspects of quality of life or function that are influenced by health status, and it is composed of distinct dimensions (ie, physical, psychological, and social aspects) that can be measured.[1,2] In patients with Parkinson's disease (PD), HRQOL is an important focus of clinical practice and in treatment outcome studies.[3,4] An outright cure for the disease still remains elusive, leaving patients with the challenges of living with a chronic medical condition. Thus, many potential factors could impair HRQOL in PD patients. Notably, motor dysfunction and depression are widely recognized as the main contributors to impairment of HRQOL in this chronic condition.[5–7]

Apathy is a common neuropsychiatric symptom that is increasingly recognized as another common

***Correspondence to:** Dr. Julián Benito-León, Avda. de la Constitución 73, portal 3, 7° Izquierda, E-28821 Coslada, Madrid, Spain; jbenitol@meditex.es

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behavioral feature of PD.[8] It is generally defined as a decrease in goal-directed behavior attributable to loss of motivation.[8] Existing work supports the view that apathy and depression are distinct though sometimes overlapping constructs.[8] Although there is growing evidence that apathy is one of the core nonmotor features of PD,[8] little is known about its impact on HRQOL in the early stages of PD. There have been surprisingly few studies that have assessed this association in PD. For example, in the PRIAMO study, a multicenter Italian survey involving 1072 PD patients with a mean disease duration of 5.1 years, apathy was the symptom most associated with lower HRQOL.[9] One possible limitation of that study was that apathy was only assessed using 3 questions with dichotomous (yes/no) answers, without recourse to a validated instrument.[9] In a study by Bottini et al, apathy was assessed in 57 PD patients with a mean disease duration of 7.5 years. In that study,[10] the patients who reported apathy scored worse on the Parkinson's Disease and Quality of Life instrument than did those without apathy.

The impact of apathy on HRQOL in recently diagnosed PD therefore has not been systematically investigated. We examined the contribution of apathy to HRQOL in a large representative Spanish sample of recently diagnosed PD patients, using the Lille Apathy Rating Scale (LARS), a new instrument for detecting apathy.[11] We hypothesized that apathy would be independently associated with decreased HRQOL in recently diagnosed PD cases.

Patients and Methods

General Study Design

The ANIMO Group was constituted in 2007 by a group of Spanish neurologists with expertise in PD. In that year, a study of apathy in a representative sample of patients with recently diagnosed PD was proposed: the ANIMO study. We sampled a series of patients from 102 Spanish PD outpatient clinics (see Acknowledgments section). These outpatient clinics were in 82 communities throughout Spain, thereby representing a broad geographic population. We chose these PD outpatient clinics because they maintain a computer-based registry of PD patients. We asked the participant neurologists to recruit a minimum of 6 consecutive PD patients who were coming to their clinic and who met the following criteria: PD diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria,[12] within 2 years of inclusion, and age $\geq$ 30 years. Patients with other types of parkinsonism were excluded, as were those with dementia according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) criteria.[13] A diagnosis of dementia was established on the basis of the medical history, an interview with the patient and a family member or caregiver, a general medical examination, results from laboratory tests, and diagnostic neuroimaging when needed. We excluded dementia patients because different studies have concluded that the validity of self-reported HRQOL is uncertain in dementia patients.[14,15] In the early stages of dementia, some patients may give overly optimistic ratings of their capabilities and activities.[16]

For the purposes of this study, we asked the outpatient clinical neurologists to provide relevant medical information related to these patients, including age, sex, educational level, and medications. In addition, for each patient, the study physicians generated a list of all existing and past medical illnesses, detailed by organ systems, and a list of current and past treatments. We used the Cumulative Illness Rating Scale (CIRS) to measure the burden of medical comorbidity.[17]

Individuals received a clinical psychiatric interview,[18] with current and past psychiatric diagnoses established according to the DSM-IV-TR using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders. Diagnoses of symptomatic depression included major depressive episode, minor depression, and dysthymia. Depressive disorders in full remission (asymptomatic) were classified as nondepressed.

The Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale[19] and Hoehn and Yahr stage,[20] both rated in the "on" state, provided measures of motor deficits and disease progression, respectively.

All procedures were approved by the Ethics Committee of "Complejo Asistencial Universitario" in Burgos, Spain. Written (signed) informed consent was obtained from all participants on enrollment. The study was designed as a cross-sectional survey. There were no treatment interventions during the course of this study.

Instruments

The EuroQoL is a standardized and validated generic measure of HRQOL that can be used in both healthy populations as well as in different groups of diseases,[21,22] It is a useful measure of HRQOL in PD, reflecting severity and complications of the disease.[4,23] The EuroQoL consists of 2 sections.[24] The first section (the EQ-5D) comprises 5 questions (items) relating to current problems in the dimensions "mobility," "self-care," "usual activities," "pain/discomfort," and "anxiety/depression." Responses in each dimension are divided into 3 ordinal levels coded as: (1) no problems, (2) moderate problems, and (3) extreme problems. This part, called the EQ-5D descriptive system, provides a 5-dimensional description of health status. The EQ-5D generates 243 theoretically possible health states.

Calculation of the EuroQol-5D index score was performed according to European recommendations.[25] These scores express HRQOL quantitatively as a fraction of perfect health, with a score of 1 representing perfect health, a score of 0 representing death, and negative scores (minimum score −0.109) representing health states considered worse than death. The second section of the EuroQoL is a vertical visual analog scale (VAS), similar to a thermometer, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ VAS records the respondent's self-rated evaluation of health status (EQ VAS score).[24]

Apathy was assessed with the LARS.[11] The LARS includes 33 items, divided into 9 domains (ie, reduction in everyday productivity, lack of interest, lack of initiative, extinction of novelty seeking, motivation, blunting of emotional responses, lack of concern, poor social life, and extinction of self-awareness). Each domain contributes equally to the global score. Items are scored yes/no except for the first 3 questions, which are scored on a 5-point Likert-type scale. Global LARS scores range from −36 to +36, with higher scores indicating greater apathy.[11] Standard validity indices showed that the LARS is sensitive and capable of distinguishing between apathy and depression.[11] Apathy was defined here as a score on the LARS ≥ -16.[11] Missing data were imputed by an individual mean method if missing data were ≤20% of the total.[26,27]

Statistical Analyses

Statistical analyses were performed in SPSS Version 18.0 (SPSS, Inc., Chicago, IL). All P values are 2 tailed, and we considered $P < .05$ as significant. Proportions were compared using chi-square test or Fisher's exact test. As the continuous variables were not normally distributed, the Mann–Whitney test was used. Correlation coefficients were Spearman rank correlation coefficients. An association was considered high if the correlation coefficient (r_S) was >0.50, moderate if 0.35–0.50, and weak if <0.35.[28]

As the number of respondents reporting "extreme problems" was small for all EQ-5D dimensions, the levels "moderate problems" and "extreme problems" were combined into 1 category ("problems"). On the other hand, as the EQ VAS score was not normally distributed (Kolmogorov–Smirnov, $P < .001$), even after log-transformation, linear regression analysis was not possible. Therefore, to assess the effects of possible confounders, we divided the EQ VAS score into 2 strata (lowest quartile score [worse HRQOL] vs all other scores [reference]).

An EuroQol-5D index score of 0.89, obtained from population references in Spain, was used as the cutoff point for this study.[22] Multivariate logistic regression models were fitted to study (1) the association between EuroQol-5D index score < 0.89 (lower HRQOL) versus ≥0.89 (reference), the dependent variable, and apathy, the independent variable; and (2) the association between the lowest quartile of the EQ VAS (reference = all other scores), the dependent variable, with apathy, the independent variable. Significant associated covariates included age, sex, geographical area (rural vs urban), educational level (illiterate, primary studies, secondary or higher studies), marital status (single, married, widowed, and separated/divorced), occupational status (employed/unemployed [retired was classified as unemployed]), presence of caregiver, symptomatic depression without apathy (from now on will be referred to as "depression only"), UPDRS motor subscale score, Hoehn and Yahr stage, predominant PD motor impairment laterality (right, left, and both), motor fluctuations, dopaminergic agonist use, levodopa use, and comorbidity (CIRS total score). We began with an unadjusted model. Then, in an adjusted model, we considered all variables that in univariate analyses were associated with either apathy or EuroQol-5D index score < 0.89 (lower HRQOL; reference ≥ 0.89) or the lowest quartile of the EQ VAS (reference = all other scores). These analyses generated odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Of the 677 PD patients who were deemed eligible for the study, 557 (82.3%) were finally chosen. The remaining 120 PD patients (17.7%) were excluded because of insufficient medical information (eg, missing values on 1 or more UPDRS items). We compared the final sample of 557 cases with the 120 cases with insufficient medical information, and they were similar in age (68.8 ± 9.7 vs 67.7 ± 9.4 years, Mann–Whitney; $P = .14$) and sex (336 men [60.3%] vs 67 men [55.8%]; $\chi^2 = 0.363$, $P = .41$). Imputation for missing data of the LARS was carried out in 47 subjects (8.4% of the final sample). The 557 PD patients were recruited between March 2007 and January 2009.

Mean age of PD patients was 68.8 ± 9.7 years, and 336 were men (60.3%). PD duration was 1.3 ± 0.6 years. Apathy (LARS score ≥ −16) was diagnosed in 291 patients (52.2%) and any type of depression in 250 patients (44.9%). Concomitant apathy and symptomatic depression was detected in 170 (30.5%), apathy without symptomatic depression in 121 patients (21.7%), and depression only in 80 (14.4%). Of depressive patients, 31 (12.4%) had major depression, 161 (64.4%) minor depression, and 58 (23.2%) dysthymia. Three hundred and fifty-seven patients (64.1%) were on dopaminergic agonists, 332 (59.6%) on levodopa (mean dose, 385.4 ± 209.2 mg; range, 20–1250 mg), and 235 (42.2%) on antidepressants. Among dopaminergic agonists, 255 patients (45.8%)

TABLE 1. Demographic and clinical characteristics of cohort stratified by apathy status

	Nonapathetic (n = 266)	Apathetic (n = 291)
Age[a]	67.4 ± 10.2 (68.0)	70.1 ± 9.1 (71.0)
Sex (male)	157 (59.0%)	179 (61.5%)
Geographical area		
Rural area	101 (38.0%)	96 (33.0%)
Urban area	165 (62.0%)	195 (67.0%)
Educational level[a,c]		
Illiterate	11 (4.1%)	27 (9.3%)
Primary studies	157 (59.0%)	193 (66.8%)
≥ Secondary studies	98 (36.8%)	69 (23.9%)
Marital status[c]		
Single	18 (6.8%)	21 (7.2%)
Married or cohabitant	198 (74.7%)	204 (70.1%)
Widowed	41 (15.5%)	56 (19.2%)
Separated or divorced	8 (3.0%)	10 (3.4%)
Occupational status		
Employed	48 (18.0%)	40 (13.7%)
Unemployed	218 (82.0%)	251 (86.3%)
Presence of caregiver[b,c]	128 (48.7%)	200 (69.7%)
Presence of depression only[b]	80 (30.1%)	0 (0.0%)
UPDRS motor score[b]	17.1 ± 8.5 (15.0)	24.8 ± 11.3 (24.0)
Hoehn & Yahr stage[b]		
I	170 (63.9%)	113 (38.8%)
II	79 (29.7%)	132 (45.4%)
III	16 (6.0%)	42 (14.4%)
IV	1 (0.4%)	4 (1.4%)
Predominant laterality of motor symptoms[b]		
Right	142 (53.4%)	148 (50.9%)
Left	105 (39.5%)	91 (46.4%)
Both	19 (7.1%)	52 (17.9%)
Presence of motor fluctuations[a,c]	24 (9.1%)	48 (16.6%)
Dopaminergic agonist use	168 (63.2%)	189 (64.9%)
Levodopa use[b]	128 (48.1%)	204 (70.1%)
Comorbidity (CIRS-G score)[b]	3.6 ± 2.8 (3.0)	5.0 ± 3.6 (4.0)
EuroQol-5D[d]		
Problems in dimension "mobility"[b]	105 (39.5%)	194 (66.7%)
Problems in dimension "self-care"[b]	52 (19.5%)	133 (45.7%)
Problems in dimension "usual activities"[b]	78 (29.3%)	186 (63.9%)
Problems in dimension "pain/discomfort"[b]	118 (44.4%)	189 (64.9%)
Problems in dimension "anxiety/depression"[b]	62 (23.3%)	182 (62.5%)
EQ VAS score[b]	68.1 ± 16.2 (70.0)	56.9 ± 18.6 (60.0)
EuroQol-5D index score[b]	0.83 ± 0.17 (0.87)	0.64 ± 0.26 (0.66)

Mean ± SD (median) and frequency (%) are reported. Mann–Whitney *U* test was used for comparisons of continuous data and the χ_2 test or Fisher p for proportions. Cumulative Illness Rating Scale-Geriatrics = CIRS-G score.
[a]$P < .01$;
[b]$P < .001$;
[c]Data on some participants were missing;
[d]percentage of patients scoring moderate or extreme problems on each of the EuroQol-5D dimensions.

were on pramipexole (mean dose, 2.06 [2.1] ± 0.9 mg base vs 1.86 [2.1] ± 0.9 mg base; 2.94 [3] ± 1.28 mg salt vs 2.65 [3] ± 1.28 mg salt), 53 (9.5%) on ropinirole (mean dose, 10.20 ± 5.65 mg; range, 2.0–24 mg), 36 (6.5%) on rotigotine (mean dose, 8.22 ± 3.30 mg; range, 2–16 mg), and 1 (0.2%) on cabergoline (2 mg daily). Ten patients (1.8%) were receiving both pramipexole and rotigotine, 1 patient (0.2%) pramipexole and cabergoline, and 1 patient (0.2%) ropinirole and rotigotine.

Compared with patients with apathy, nonapathetic patients were younger, more educated, and with lower motor severity impairment and rates of associated comorbid medical conditions (Table 1). In addition, they reported fewer problems in each one of the dimensions of the EQ-5D (Table 1). Mean scores on the EuroQol-5D index score and on the EQ VAS in apathetic recently diagnosed PD patients were significantly lower than those in nonapathetic patients (Table 1).

Using the dichotomized EuroQol-5D index score, there were significant differences between those who scored <0.89 (lower HRQOL) versus those who scored ≥0.89 (Table 2). Overall, as expected, participants who scored <0.89 were significantly older, less educated, and had higher motor severity impairment and more medical comorbidity than participants who scored ≥0.89. In addition, they were more likely to require a caregiver and to be unemployed (Table 2). After adjusting for age in years, sex, geographical area, educational level, occupational status, presence of caregiver, depression only, UPDRS motor score, Hoehn & Yahr stage, predominant laterality of motor symptoms, motor fluctuations, levodopa use, and comorbidity, apathetic PD patients were 2.49 times more likely to have lower HRQOL (EuroQol-5D index score < 0.89) than were nonapathetic PD patients (OR, 2.49; 95% CI, 1.49–4.15; $P < .01$; Table 3).

As expected, those who rated their health state in the lowest quartile of the EQ VAS scored significantly higher on the LARS than those who rated their health status in the remaining quartiles (Table 4). Further, logistic regression analysis, adjusted for age in years, sex, educational level, marital status, occupational status, presence of caregiver, depression only, UPDRS motor score, Hoehn & Yahr stage, predominant laterality of motor symptoms, motor fluctuations, levodopa use, and comorbidity, showed that apathetic PD patients tended to rate their health state significantly lower on the EQ VAS than did nonapathetic PD patients (Table 5).

The correlations observed between EuroQoL and LARS dimensions are presented in Table 6. Overall, there were significant, although weak to moderate, correlations between EuroQoL and LARS dimensions.

Imputation of data by an individual mean method may have improved the average apathy score. To assess this possibility, we conducted a sensitivity analysis. We

TABLE 2. Demographic and clinical characteristics of cohort stratified by EuroQol-5D index score

	EQ-5D < 0.89 (n = 422)	EQ-5D ≥ 0.89 (n = 135)
Age[c]	69.7 ± 9.3 (71.0)	66.0 ± 10.4 (67.0)
Sex (male)[a]	243 (57.6%)	93 (68.9%)
Geographical area[a]		
Rural area	159 (37.7%)	38 (28.1%)
Urban area	263 (62.3%)	97 (71.9%)
Educational level[a,d]		
Illiterate	28 (6.7%)	10 (7.4%)
Primary studies	277 (66.0%)	73 (54.1%)
≥ Secondary studies	115 (27.4%)	52 (38.5%)
Marital status[d]		
Single	25 (5.9%)	14 (10.4%)
Married or cohabitant	301 (71.5%)	101 (74.8%)
Widowed	80 (19.0%)	17 (12.6%)
Separated or divorced	15 (3.6%)	3 (2.2%)
Occupational status[a]		
Employed	59 (14.0%)	29 (21.5%)
Unemployed	363 (86.0%)	106 (78.5%)
Presence of caregiver[c,d]	266 (63.9%)	62 (46.3%)
Presence of depression only	63 (14.9%)	17 (12.6%)
UPDRS motor score[c]	23.1 ± 11.0 (22.0)	14.8 ± 7.3 (14.0)
Hoehn & Yahr stage[c]		
I	193 (45.7%)	90 (66.7%)
II	167 (39.6%)	44 (32.6%)
III	57 (13.5%)	1 (0.7%)
IV	5 (1.2%)	0 (0.0%)
Predominant laterality of motor symptoms		
Right	217 (51.4%)	73 (54.1%)
Left	145 (34.4%)	51 (37.8%)
Both	60 (14.2%)	11 (8.1%)
Presence of motor fluctuations[b,d]	66 (15.7%)	6 (4.4%)
Dopaminergic agonist use	279 (66.1%)	78 (57.8%)
Levodopa use[c]	278 (65.9%)	54 (40.0%)
Comorbidity (CIRS-G score)[c]	4.7 ± 3.4 (4.0)	3.1 ± 2.6 (3.0)
Lille Apathy Rating Scale total score[c]	−12.5 ±14.7 (−6)	−20.2 ±10.3 (−21)

Mean ± SD (median) and frequency (%) are reported. Mann–Whitney *U* test was used for comparisons of continuous data and χ_2 test or Fisher *p* for proportions. Cumulative Illness Rating Scale-Geriatrics = CIRS-G score.
[a]$P < .05$;
[b]$P < .01$;
[c]$P < .001$;
[d]Data on some participants were missing.

restricted the analysis to participants with complete LARS; in these analyses, we also found that apathy was associated with an EuroQol-5D index score < 0.89 in unadjusted (OR, 3.25; 95% CI, 2.10–5.02; $P < .001$) and adjusted (OR, 2.43; 95% CI, 1.41–4.18; $P = .001$) models. Similarly, apathy was associated with the lowest quartile of the EQ VAS in unadjusted (OR, 3.42; 95% CI, 2.26–5.16; $P < .001$) and adjusted (OR, 3.14; 95% CI, 1.82–5.44; $P < .001$) models.

Discussion

In this large multicenter nationwide cross-sectional study, apathy was associated with lower HRQOL in recently diagnosed PD. As we hypothesized, apathetic PD patients had an overall EuroQol-5D index score that was significantly lower than that of nonapathetic patients, even after controlling for potential confounding variables. Further, apathy was independently associated with the lowest quartile (lower HRQOL) of the EQ VAS.

The results of this study have several clinical implications. Apathy may be a marker of poor HRQOL in recently diagnosed PD, even after adjusting for potential confounders, mainly depression. In addition, we also observed that apathetic PD patients reported more problems in each of the 5 dimensions of the EQ-5D. This suggests that apathy might affect all spheres of a patient's subjective health status. Second, apathy is very prevalent among recently diagnosed PD patients. In our sample, more than 50% of patients were diagnosed with apathy. This percentage is comparable to that reported in a recent study by Oguru et al,[29] who found that 60% of 150 PD patients were considered to have apathy. In the only case–control study of apathy in drug-naive patients with incident PD, apathy was found in 22.9%.[30] One important question is: why is apathy so prevalent among recently diagnosed PD patients? The pathogenesis of apathy in this population has not been elucidated, but there is some evidence that it might be caused by a ventral striatal dopaminergic deficit and depletion of serotonin and norepinephrine,[31–33] and these pathophysiological mechanisms are already found in the early phase of the parkinsonian state.[32]

There are certain limitations to our study that must be considered. First, the patients in the current study may represent a selected group of recently diagnosed PD patients (ie, patients seen in selected outpatient clinics), and hence it is questionable to what extent our results can be generalized to the entire early PD population. However, we recruited a large representative cross-section of the community-dwelling

TABLE 3. Apathy status (independent variable) and odds of EuroQol-5D index score < 0.89 (dependent variable)

	Unadjusted		Adjusted	
	Odds ratio	95% CI	Odds ratio	95% CI
Apathetic PD patients (n = 291)	3.19[b]	2.11–4.82	2.49[a]	1.49–4.15
Nonapathetic PD patients (n = 266), reference category	1.00	—	1.00	—

Adjusted for age in years, sex, geographical area, educational level, occupational status, presence of caregiver, depression only, UPDRS motor score, Hoehn & Yahr stage, predominant laterality of motor symptoms, motor fluctuations, levodopa use, and comorbidity.
[a]$P < .01$;
[b]$P < .001$.

TABLE 4. Demographic and clinical characteristics of cohort stratified by EQ-VAS quartiles

	Lowest quartile of EQ VAS (EQ VAS ≤ 50), n = 171	All other scores, n = 386
Age	70.4 ± 8.7 (71.0)	68.1 ± 10.0 (69.0)
Sex (male)[b]	88 (51.5%)	248 (64.2%)
Geographical area		
Rural area	60 (35.1%)	137 (35.5%)
Urban area	111 (64.9%)	249 (64.5%)
Educational level[b,d]		
Illiterate	16 (9.4%)	22 (5.7%)
Primary studies	118 (69.0%)	232 (60.4%)
≥ Secondary studies	37 (21.6%)	130 (33.9%)
Marital status[b,d]		
Single	14 (8.2%)	25 (6.5%)
Married or cohabitant	107 (62.6%)	295 (76.6%)
Widowed	42 (24.6%)	55 (14.3%)
Separated or divorced	8 (4.7%)	10 (2.6%)
Occupational status[c]		
Employed	16 (9.4%)	72 (18.7%)
Unemployed	155 (90.6%)	314 (81.3%)
Presence of caregiver[a,d]	112 (65.9%)	216 (56.8%)
Presence of depression only	19 (11.1%)	61 (15.8%)
UPDRS motor score[c]	25.7 ± 12.0 (25.0)	19.1 ± 9.6 (17.0)
Hoehn & Yahr stage[c]		
I	64 (37.4%)	219 (56.7%)
II	73 (42.7%)	138 (35.8%)
III	32 (18.7%)	26 (6.7%)
IV	2 (1.2%)	3 (0.8%)
Predominant laterality of motor symptoms[b]		
Right	88 (51.5%)	202 (52.3%)
Left	49 (28.7%)	147 (38.1%)
Both	34 (19.9%)	37 (9.6%)
Presence of motor fluctuations[d]	29 (17.0%)	43 (11.2%)
Dopaminergic agonist use	91 (62.3%)	239 (65.7%)
Levodopa use[a]	99 (67.8%)	201 (55.2%)
Comorbidity (CIRS-G score)[b]	5.1 ± 3.6 (4.0)	4.0 ± 3.1 (3.0)
Lille Apathy Rating Scale total score[c]	−5.1 ±14.9 (−6)	−15.6 ±13.0 (−18)

Mean ± SD (median) and frequency (%) are reported. Mann–Whitney *U* test was used for comparisons of continuous data and χ_2 test or Fisher *p* for proportions. Cumulative Illness Rating Scale-Geriatrics = CIRS-G score.
[a]$P < .05$;
[b]$P < .01$;
[c]$P < .001$;
[d]Data on some participants were missing.

population of nondemented Spanish recently diagnosed PD patients. In Spain, health care is fully state subsidized, and community-dwelling PD subjects are mostly seen by hospital-based and hospital-associated neurologists.[34–36] Second, we used a generic measure of HRQOL designed to measure quality-of-life outcomes for any disease or treatment as opposed to disease-specific dimensions. Although the EuroQoL has been shown to be a valid measure of HRQOL in PD,[4,7,21] the instrument may nevertheless not reveal the full spectrum of symptoms and impairments associated with PD. However, in the conduct of PD studies, there are few instruments better suited for quality-of-life evaluation than the EuroQoL.[4,7,23] Further, we chose the EuroQoL because of its brevity, acceptability for routine and repetitive administration, and suitability for cost-utility studies both in PD patients and in patient populations with other disease conditions. Third, there are important potentially relevant nonclinical risk factors that were not assessed in our study, including the overall quality of the PD care delivered. Fourth, residual confounding by unmeasured variables in the multivariate analyses of HRQOL determinants is possible. Fifth, the use of a cross-sectional design leaves us more susceptible to confounding variables; however, it also enables us to generate hypotheses that should be confirmed in further studies. Finally, PD patients were not evaluated using detailed neuropsychological testing. Of interest is that Pluck and Brown[37] reported that highly apathetic, nondemented PD patients performed worse than their less apathetic counterparts, especially in tasks evaluating

TABLE 5. Apathy status (independent variable) and odds of lowest quartile of EQ VAS (dependent variable)

	Unadjusted		Adjusted	
	Odds ratio	95% CI	Odds ratio	95% CI
Apathetic PD patients (n = 291)	3.75[a]	2.52–5.57	3.62[a]	2.15–6.11
Nonapathetic PD patients (n = 266), reference category	1.00	—	1.00	—

Adjusted for age in years, sex, educational level, marital status, occupational status, presence of caregiver, depression only, UPDRS motor score, Hoehn & Yahr stage, predominant laterality of motor symptoms, motor fluctuations, levodopa use, and comorbidity.
[a]$P < .001$

TABLE 6. Matrix of correlations (Spearman rank correlation coefficients) among the Lille Apathy Rating Scale and EuroQol

	EuroQoL	
Lille Apathy Rating Scale	EuroQol-5D index score	Vertical visual analog scale
Reduction in everyday productivity	0.428[b]	0.335[b]
Lack of interest	0.418[b]	0.319[b]
Lack of initiative	0.460[b]	0.373[b]
Extinction of novelty seeking	0.321[b]	0.320[b]
Motivation	0.487[b]	0.420[b]
Blunting of emotional responses	0.218[b]	0.154[b]
Lack of concern	0.210[b]	0.126[a]
Poor social life	0.352[b]	0.292[b]
Extinction of self awareness	0.288[b]	0.210[b]

[a]$P < .01$;
[b]$P < .001$.

executive functions. Our study was not designed to draw conclusions about the relationship between apathy and executive function. The presence of patients with mild cognitive impairment might have lessened the likelihood of valid ratings of the apathy. However, based on the original validation study in which the authors demonstrated that the LARS had satisfactory clinimetric properties, even with the inclusion of demented PD patients,[11] we think that such potential rating errors were likely to be low.

This study also has several strengths. First, we attempted to adjust for the effects of many potential confounders. Second, we used modern statistical methods to deal with the challenge of missing data of the LARS. People with worse apathy scores tend to be the persons with missing data. Hence, excluding them would have provided artificially better mean scores.[38] Third, we determined the impact of apathy in a population of recently diagnosed PD patients already on treatment. This avoided bias of treatment status on HRQOL. Our results may therefore be extrapolated to the PD community to some degree. Finally, weights used for the EuroQol-5D index estimation were obtained from the general population of Spain.[22]

In summary, apathy is very common in those with recently diagnosed PD and is one of the major clinical determinants of HRQOL in this disease. Clearly, apathy should be one of the primary concerns among clinicians who provide treatment to individuals affected by PD. Furthermore, in-depth assessment of apathy should be incorporated as an outcome measure in clinical trials. ■

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