Distribution and impact on quality of life of the pain modalities assessed by the King’s Parkinson’s disease pain scale

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In Parkinson’s disease, pain is a prevalent and complex symptom of diverse origin. King’s Parkinson’s disease pain scale, assesses different pain syndromes, thus allowing exploration of its differential prevalence and influence on the health-related quality of life of patients. Post hoc study 178 patients and 83 matched controls participating in the King’s Parkinson’s disease pain scale validation study were used. For determining the respective distribution, King’s Parkinson’s disease pain scale items and domains scores = 0 meant absence and ≥1 presence of the symptom. The regular scores were used for the other analyses. Health-related quality of life was evaluated with EQ-5D-3L and PDQ-8 questionnaires. Parkinson’s disease patients experienced more pain modalities than controls. In patients, Pain around joints (King’s Parkinson’s disease pain scale item 1) and Pain while turning in bed (item 8) were the most prevalent types of pain, whereas Burning mouth syndrome (item 11) and Pain due to grinding teeth (item 10) showed the lowest frequency. The total number of experienced pain modalities closely correlated with the PDQ-8 index, but not with other variables. For all pain types except Pain around joints (item 1) and pain related to Periodic leg movements/RLS (item 7), patients with pain had significantly worse health-related quality of life. The influence of pain, as a whole, on the health-related quality of life was not remarkable after adjustment by other variables. When the particular types of pain were considered, adjusted by sex, age, and Parkinson’s disease duration, pain determinants were different for EQ-5D-3L and PDQ-8. King’s Parkinson’s disease pain scale allows exploring the distribution of the diverse syndromic pain occurring in Parkinson’s disease and its association with health-related quality of life.

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INTRODUCTION

Pain is a common non-motor symptom of Parkinson’s disease (PD), frequently undeclared and, consequently, undertreated.1,2 Nowadays, it is well known that different types of pain can be recognized in PD patients,3,4 a fact that makes appropriate assessment and management of this symptom difficult. Although several studies showed a deleterious effect of pain on the health-related quality of life (HRQoL), the specific effect of pain on quality of life in people with PD has not been tested with specific pain measures and is partially unclear.5,6 HRQoL refers to those aspects of the individuals’ quality of life (QoL) related with health status and care and, therefore, is a more restricted concept than ‘global QoL’. As there is no a universally accepted definition of HRQoL, we define here this construct as: “the perception and evaluation, by patients themselves, of the impact caused on their life by the disease and its consequences”.7

Determinant factors (e.g., depression, disability, and insomnia) influence the HRQoL and, therefore, the association between these factors and the HRQoL is close and consistent. On the other hand, modification of the determinant factors will result in changes of the HRQoL. Thus, their identification and appropriate management may be crucial for improving the patients’ QoL. Pain is a widely recognized determinant of QoL in any setting and also in PD.6,8 a condition in which pain is a complex and highly prevalent symptom.9

Recently, the King’s Parkinson’s Disease Pain Scale (KPPS) has been validated as the first specific rating scale to evaluate the burden of pain in the context of PD. The KPPS assesses seven different domains corresponding to the diverse modalities of pain identified in PD. In the first validation study, a high correlation was found between the KPPS total score and the summary indexes of a generic (EQ-5D-3L) and a PD-specific (PDQ-8) HRQoL instrument.10

Taking advantage of the existing data from the validation study and the close relationships between pain burden and QoL, we explored in the present study the distribution in the sample of the different types of pain assessed by the KPPS and how they impact on the HRQoL of PD patients.

RESULTS

The characteristics of the sample are shown in Table 15 (Supplementary material). Most of patients (71.35%) were in

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In patients with PD, only musculoskeletal pain was significantly more frequent in women (97% vs. 77.7%; p < 0.001). Modalities of nocturnal pain (dysskinetic and pain related with "off dystonia") tended to decrease with age, but did not reach statistical significance after correction for multiple testing (p < 0.025 needed). Items 5 and 6 (fluctuation-related pains) and item 14 (radicular pain), however, were significantly less frequent in patients with higher age at onset of PD (p = 0.002–0.015). The three components of the nocturnal pain domain were significantly more frequent in patients with longer disease duration (p = 0.014 to <0.001). No other significant differences were observed regarding these variables.

The total number of experienced syndromic pain was not statistically different by gender (3.8, men; 4.4, women; p = 0.10). This total number correlated moderately with SCOPA-Motor (rS = 0.38), clinical impression of severity index for PD (CISI-PD) (rS = 0.37) and EQ-SD-3L Index (S = 0.41), and highly with the PDQ-8 Index (rS = 0.55) (all coefficients, p < 0.001). Correlation values with age, years of education, age at onset, PD duration, HY, and levodopa-equivalent daily dose were negligible or weak (rS < 0.30).

The differences in HRQoL indexes between patients with and without the diverse pain modalities is displayed in Table 3. Differences were significant, even after correction for multiple comparisons, for all items except items 1 (Pain around joints) and 7 (Periodic leg movements or Restless legs syndrome-associated pain). To be highlighted, both HRQoL indexes showed similar trends in this analysis, although differences between them were observed. The correlation of the HRQoL indexes with the KPPS dimensions and total score are shown in Table 25 (Supplementary material). As a whole, the strength of the association with the KPPS items was weak, with some items showing moderate values with the EQ-SD-3L (KPPS item 1; rS = 0.36; p < 0.001) and PDQ-8 indexes (KPPS items 3, 12, 13, and 14; rS = 0.35–0.41; p < 0.001). Coefficient values indicated a close and similar association between the KPPS total score and both HRQoL indexes.

The results of the multiple regression models are shown in Table 4. In the phase 1, the influence of pain (KPPS) on the generic HRQoL (EQ-SD-3L Index) was just at the limit of the statistical significance after controlling for the other factors in the model, with functional state (SCOPA-Motor ADL) and depression (HADS-Depression) as the only significant variables influencing the generic HRQoL. For the model with the specific PDQ-8, only depression, ADL, and sleep (PDSS-2) were significant.

### Table 1. Descriptive statistics of the assessments in the study

| Assessment | Patients | | | | Controls | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Mean | SD | Med. | Range | | Mean | SD | Med. | Range |
| SCOPA-motor scale | 17.38 | 10.28 | 15 | 1–65 | | | | | |
| NMSS | 60.71 | 44.31 | 48 | 0–235 | | | | | |
| CISI-PD | 6.54 | 3.93 | 6 | 0–19 | | | | | |
| HADS-anxiety | 6.17 | 4.56 | 5 | 0–20 | | | | | |
| HADS-depression | 5.44 | 3.96 | 5 | 0–18 | | | | | |
| EQ-SD-3L | 0.52 | 0.28 | 0.62 | −0.43–1 | | | | | |
| PDQ-8 | 27.84 | 20.28 | 25 | 0–93.75 | | | | | |
| PDSS-2 | 18.25 | 11.20 | 16.50 | 0–51 | | | | | |
| VAS pain | 32.92 | 23.84 | 27.67 | 0–100 | | | | | |
| King’s PD pain scale | | | | | | | | |
| 1. Musculoskeletal pain | 6.02 | 4.07 | 6 | 0–12 | | | | | |
| 2. Chronic pain | 3.37 | 5.53 | 0 | 0–24 | | | | | |
| 3. Fluctuation-related pain | 5.27 | 8.26 | 0 | 0–36 | | | | | |
| 4. Nocturnal pain | 4.91 | 5.87 | 3 | 0–24 | | | | | |
| 5. Oro-facial pain | 0.97 | 3.00 | 0 | 0–22 | | | | | |
| 6. Discolouration, OS | 2.29 | 4.49 | 0 | 0–24 | | | | | |
| 7. Radicular pain | 2.36 | 3.53 | 0 | 0–12 | | | | | |
| KPPS Total score | 25.19 | 22.14 | 17 | 0–102 | | | | | |

SD standard deviation, Med median, SCOPA scales for outcomes in Parkinson’s disease, NMSS non-motor symptoms scale, CISI-PD clinical impression of severity index–Parkinson’s disease, HADS hospital anxiety and depression scale, EQ-SD-3L EuroQol-5 dimensions-3 levels, PDQ-8 Parkinson’s disease questionnaire-8 items, PDSS-2 Parkinson’s disease sleep scale version 2, VAS visual analog scale, Discolouration, OS discolouration; edema/Swelling, KPPS King’s Parkinson’s disease pain scale
determinants. For the phase 2 models, musculoskeletal pain, fluctuation-related pain, and PD duration were the factors significantly and independently influencing the EQ-5D-3L index, whereas nocturnal pain, peripheral discoloration/oedema related pain, and (again) PD duration were the key factors for the PDQ-8 index.

**DISCUSSION**

Pain has been recognized in 40–85% of PD patients, and is a complex manifestation in this condition that expresses a variety of syndromic pain, including musculoskeletal and visceral nociceptive pain, central and peripheral neuropathic pain, and other modalities. Apart from this, 25–64% of PD patients are thought to experience pains unrelated to this disorder.

This study was carried out on a sample of PD patients systematically characterized by declaring otherwise unexplained pain, without dementia or recognized disorders causing pain, and matched controls. Using the KPPS, it was possible to explore the distribution of the different modalities of pain assessed by this scale in both groups and the main findings were:

1. The average number of pain types present in PD patients (n = 4) was double than in controls (n = 2). The maximum number of pain modalities experienced was significantly higher in the patients group (13/14 vs. 9/14).

2. In both groups, the most prevalent modality of pain was musculoskeletal pain, whereas the lowest were the oro-facial pains.

3. Nocturnal pain (pain while turning in bed and pain related to periodic leg movements/restless legs syndrome) was significantly more prevalent in patients.

Musculoskeletal pain may be a dominant symptom in early PD stages and has been attributed the cause of 40–90% of the reported pain, as well as the most prevalent type (41–70%), followed by dystonic pain (40–48%), radicular-neuropathic pain (14–35%), central neuropathic pain (22–36%), and other modalities pains (5.7%). The corresponding figures for the present study were: musculoskeletal, 84.8%; dystonic, 33.2%; radicular, 46.1%; central neuropathic, 31.5%; and oro-facial pain, 20.8%. The origin of musculoskeletal pain in PD is complex and is a mixture of nociceptive and neuropathic elements complicated by local joint related pain as well as parkinsonian rigidity and postures such as dystonia. The recently reported PANDA study for instance, reported efficacy of the active drug (oxycodeone/naloxone combination) on musculoskeletal pain when applying

### Table 2. Types of pain prevalence in the sample

| King's Parkinsons' disease pain scale items | Prevalence (%) | PD patients | Controls | p     |
|-------------------------------------------|----------------|-------------|-----------|-------|
| Domain 1: musculoskeletal pain             |                |             |           |       |
| 1. Pain around joints                      | 84.8           | 69.9        | 0.005     |       |
| Domain 2: chronic pain                     |                |             |           |       |
| 2. Pain deep within the body               | 31.5           | 18.1        | 0.023     |       |
| 3. Pain related to internal organ          | 23.0           | 14.5        | 0.11      |       |
| Domain 3: fluctuation-related pain         |                |             |           |       |
| 4. Dyskinetic pain                         | 18.5           | 4.8         | 0.003     |       |
| 5. "Off" dystonia in a region              | 33.2           | 6.0         | <0.0001   |       |
| 6. Generalized "off" period pain           | 25.8           | 4.8         | 0.0001    |       |
| Domain 4: nocturnal pain                   |                |             |           |       |
| 7. PLM or RLS-associated pain              | 29.2           | 13.3        | 0.005     |       |
| 8. Pain while turning in bed               | 48.3           | 16.9        | <0.0001   |       |
| Domain 5: Oro-facial pain                  |                |             |           |       |
| 9. Pain when chewing                       | 8.4            | 1.2         | 0.023     |       |
| 10. Pain due to grinding teeth             | 7.3            | 2.4         | 0.11      |       |
| 11. Burning mouth syndrome                 | 5.1            | 1.2         | 0.13      |       |
| Domain 6: discoloration; edema/swelling    |                |             |           |       |
| 12. Burning pain in the limbs              | 21.9           | 9.6         | 0.016     |       |
| 13. Lower abdominal pain                   | 19.1           | 8.43        | 0.027     |       |
| Domain 7: radicular pain                   |                |             |           |       |
| 14. Shooting pain/pins and needles         | 46.1           | 28.9        | 0.008     |       |

Benjamini–Hochberg correction for multiple comparisons: for prevalence (n = 14): p < 0.026.

**PD Parkinson's disease, PLM periodic leg movements, RLS restless legs syndrome**

### Table 3. Types of pain and quality of life indexes in Parkinson's disease patients

| King's Parkinsons' disease pain scale items | EQ-5D-3L | PDQ-8 |
|-------------------------------------------|----------|-------|
| 1. Pain around joints                      | 0.59 ± 0.25 | 0.51 ± 0.29 | 0.1 | 25.11 ± 19.62 | 28.33 ± 20.42 | 0.43 |
| 2. Pain deep within the body               | 0.57 ± 0.23 | 0.41 ± 0.35 | 0.006 | 24.18 ± 18.72 | 35.83 ± 21.40 | 0.0004 |
| 3. Pain related to internal organ          | 0.55 ± 0.26 | 0.41 ± 0.33 | 0.005 | 24.06 ± 18.85 | 40.47 ± 20.00 | <0.0001 |
| 4. Dyskinetic pain                         | 0.57 ± 0.25 | 0.31 ± 0.32 | <0.0001 | 24.91 ± 19.53 | 40.72 ± 18.68 | <0.0001 |
| 5. "Off" dystonia in a region              | 0.55 ± 0.29 | 0.46 ± 0.27 | 0.007 | 25.03 ± 20.76 | 33.53 ± 18.15 | 0.001 |
| 6. Generalized "off" period pain           | 0.57 ± 0.25 | 0.39 ± 0.33 | 0.0005 | 24.53 ± 18.30 | 37.36 ± 22.76 | 0.0008 |
| 7. PLM or RLS-associated pain              | 0.54 ± 0.28 | 0.48 ± 0.30 | 0.13 | 25.79 ± 19.48 | 32.81 ± 21.49 | 0.038 |
| 8. Pain while turning in bed               | 0.58 ± 0.26 | 0.45 ± 0.29 | 0.0001 | 20.18 ± 17.56 | 36.05 ± 19.87 | <0.0001 |
| 9. Pain when chewing                       | 0.54 ± 0.28 | 0.35 ± 0.31 | 0.017 | 26.23 ± 19.50 | 45.42 ± 20.99 | 0.001 |
| 10. Pain due to grinding teeth             | 0.53 ± 0.28 | 0.37 ± 0.32 | 0.011 | 26.61 ± 19.48 | 43.51 ± 24.39 | 0.011 |
| 11. Burning mouth syndrome                 | 0.53 ± 0.28 | 0.34 ± 0.32 | 0.014 | 26.26 ± 19.35 | 57.64 ± 13.63 | 0.0001 |
| 12. Burning pain in the limbs              | 0.55 ± 0.26 | 0.40 ± 0.33 | 0.001 | 23.99 ± 18.44 | 41.59 ± 20.81 | <0.0001 |
| 13. Lower abdominal pain                   | 0.55 ± 0.27 | 0.39 ± 0.32 | 0.0004 | 24.76 ± 19.73 | 40.90 ± 17.38 | <0.0001 |
| 14. Shooting pain/pins and needles         | 0.56 ± 0.27 | 0.47 ± 0.30 | 0.01 | 21.88 ± 18.08 | 34.83 ± 20.58 | <0.0001 |

Benjamini–Hochberg correction for multiple comparisons: for prevalence (n = 28): p < 0.025, where 'm' is the number of tests considered.
In the present study, the sum of different types of other constructs in the study was observed with the PDQ-8 Index study, a proportion of PD patients receiving analgesics was 55.1% in our examination, or PD stage.3, 19 with factors like age at diagnosis, disease duration, motor complications13, 20 or disease progression,21 but no correlation between severity of pain and those variables.10 The only close association between number of different types of pain and other constructs in the study was observed with the PDQ-8 Index \( r_5 = 0.55 \). Other studies have found relationships between pain and motor complications15, 20 or disease progression,21 but no with factors like age at diagnosis, disease duration, motor examination, or PD stage.3, 19–21

At any setting, there is a wide range of factors influencing HRQoL as, for example, depression, disability, sleep disorders, and pain. In PD many of these determinant factors are present, frequently in a combined and variable manner, so that personalized analysis is needed to identify the most important ones and establish the priority order for intervention. Pain has been identified as a major correlate and a determinant factor of HRQoL in PD.6, 15, 22–25 Nonetheless, this finding is not uniform and several studies did not report an effect of pain on the HRQoL in PD patients. For instance, Schrag et al. found no difference between the U.K. general population and patients with PD on the relationship between pain and HRQoL.5 and pain did not appear among the HRQoL determinants in other studies.26 However, characteristics of the samples (age, disease duration, and education level) and instruments applied for measuring both pain and HRQoL in these studies differ from the present one. Furthermore, a specific validated instrument for assessment of pain in PD was not used in these studies.

In the present study, we have found that most of the pain modalities included in the KPPS have an effect on HRQoL, with exception to musculoskeletal pain and pain related to periodic leg movements/restless legs syndrome (Table 3). Pain, represented by the total KPPS score, however, did not appear as a determinant of HRQoL or showed only a modest effect after adjustment by other variables (Table 4). In the study by Rahman et al. the presence or absence of pain, globally considered, did not condition a significant difference on HRQoL estimated with the PDQ-39, although showed an effect in the regression analysis. Gallagher et al. using a visual analog scale for measuring pain, observed a high correlation with the PDQ-39 index, although this relationship disappeared after adjustment with motor and non-motor variables. A similar fact, although in contrary direction (appearing as significant independent effect on the EQ-5D-3L model, whereas

The KPPS,12 Thus, reports of pain symptoms being dominated by musculoskeletal element is not surprising and is consistent with published data.

In a study, chronic pain was found in 61.8% of PD patients declaring pain,15 whereas in the present study (KPPS items 2 and 3) was present in 54.5%. In the same vein, it has been found that 74–82% of patients had three or less types of pain,3, 14 whereas this proportion was 51.8% in the present study. Differences can be explained by the selection of patients for the present study and by the content of the KPPS, which explores modalities of pain not included in other rating scales, further confirming the need for the use of validated specific instruments such as the KPPS. The proportion of PD patients receiving analgesics was 55.1% in our study, a figure quite close to the 52.4% found by Broen et al.9

Although the prevalence and severity of pain in PD has been found to be higher in women,3, 15–17 this finding is not universal.16, 19 In the present study, the sum of different types of pain was mildly higher in women, but the difference was not statistically significant. The correlations between number of experienced types of pain and other variables in the study were low or moderate as a whole and lower than the correlations between severity of pains and those variables.10 The only close association between number of different types of pain and other constructs in the study was observed with the PDQ-8 Index \( r_5 = 0.55 \). Other studies have found relationships between pain and motor complications15, 20 or disease progression,21 but no with factors like age at diagnosis, disease duration, motor examination, or PD stage.3, 19–21

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Finally, concerning the influence of the different types of pain, musculoskeletal and fluctuation-related domains showed a significant independent effect on the EQ-5D-3L model, whereas

| Table 4. Results of the multiple linear regression models |
| Adjusted R² | Coeff. | SE | Significance | Beta |
| --- | --- | --- | --- | --- |
| Model 1 | | | | |
| EQ-SD-3L index | 0.43 | | | |
| SCOPA-ADL | −0.022 | 0.007 | 0.001 | −0.28 |
| HADS-Depression | −0.013 | 0.005 | 0.019 | −0.18 |
| KPPS | −0.002 | 0.001 | 0.047 | −0.17 |
| Model 2 | | | | |
| PDQ-8 index | 0.67 | | | |
| HADS-Depression | 2.51 | 0.29 | <0.001 | 0.49 |
| SCOPA-ADL | 1.43 | 0.36 | <0.001 | 0.26 |
| PDSS-2 | 0.40 | 0.11 | <0.001 | 0.22 |
| Model 3 | | | | |
| EQ-SD-3L index | 0.35 | | | |
| Musculoskeletal | −0.018 | 0.005 | <0.001 | −0.26 |
| Fluctuation-related | −0.008 | 0.003 | 0.002 | −0.24 |
| PD duration | −0.012 | 0.004 | 0.003 | −0.21 |
| Model 4 | | | | |
| PDQ-8 index | 0.31 | | | |
| Nocturnal | 0.68 | 0.26 | 0.01 | 0.20 |
| Discolouration, edema | 0.81 | 0.38 | 0.03 | 0.18 |
| PD duration | 0.70 | 0.29 | 0.02 | 0.17 |

Coef. coefficient, SCOPA-ADL scales for outcomes in Parkinson’s disease-activities of daily living, HADS hospital anxiety and depression scales, KPPS King’s Parkinson’s disease pain scale, PDSS-2 Parkinson’s Disease Sleep Scale-Version 2, PD Parkinson’s disease, PDQ-8 Parkinson’s disease questionnaire-8 items
nocturnal pain and discoloration/edema were significant for the PDQ-8 model. In addition, PD duration appeared as an independent influencing factor in both models highlighting the prominence of the disease progression over time on the patients’ HRQoL. Interestingly, two studies have now reported the efficacy of dopaminergic (rotigotine patch) and non-dopaminergic (oxycodeone with naloxone) agents on pain in randomised placebo-controlled studies. Using the KPPS, the dominant pains responding to the active agents were fluctuation related pain (rotigotine) and musculoskeletal pain (oxycodeone with naloxone) and thus a tangible effect of these therapies on HRQoL could be envisaged.12, 27

Limitations of this study are: (1) the study was not specifically designed for investigating the prevalence of pain types in PD population; (2) patients included in this study were selected on the basis of declaring pain of undetermined origin; therefore, the sample is biased (selection bias) and the distribution of pain types cannot be extrapolated to the PD population; (3) few data on pain severity are included in the present study, as most of them were explored in the pivotal KPPS validation study.10

This study is the first application of the KPPS to a sample of patients with PD and pain, and provided the opportunity of starting epidemiological analyses offering new data on the distribution and relationships of the diverse pain types occurring in PD and its links with HRQoL.

METHODS

Design

Post hoc study of the first KPPS validation study.10

Patients

One hundred seventy eight patients with a diagnosis of idiopathic PD according to the UK PD Brain Bank criteria28 experiencing otherwise unexplained pain as declared in item 10 of the NMS Questionnaire29 were included. Exclusion criteria were (1) diagnosis of parkinsonism different to idiopathic PD; (2) dementia (per internationally accepted criteria); (3) disorders causing pain unrelated to PD (e.g., severe osteoarthritis, malignancy); and (4) inability to provide consent to participate in the study. Exclusion criteria were (1) diagnosis of parkinsonism different to idiopathic PD population; (2) few data on pain severity are included in the present study, as most of them were explored in the pivotal KPPS validation study.12, 27

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Ethical aspects

The study was approved by the respective hospital ethical committees/institutional review boards. In the United Kingdom, the study was adopted by the National Institute of Health Research Central Research Network (UKCRN No 13344).17 All participants provided informed consent before their entry to the study.

Data analysis

Descriptive statistics (mean, standard deviation, median, range, percentages) were applied as needed. A single value for the applied VAS of pain (see Assessments) was obtained from (severity x frequency)/100. The frequency of each type of pain was determined considering each KPPS item score = 0 as ‘not present’ and ≥ 1 ‘present’. Main variables in the study did not show a normal distribution (Shapiro-Francia test); therefore, non-parametric tests were used for comparison and correlation. The Mann–Whitney test was used to compare HRQoL indexes between patients with and without each type of pain assessed by the KPPS. The Benjamini–Hochberg correction for multiple comparisons was applied.40 Strength of the association was analyzed with the Spearman correlation coefficient and considered ‘moderate’ for coefficient values 0.35 to 0.50, and ‘strong’ with values >0.50.

The influence of pain on patients’ HRQoL was explored in two phases: (1) Influence of pain burden and types controlling for other relevant variables in the study, and (2) Influence of each specific syndromic pain controlling the KPPS. For phase 1, multiple linear regression models were constructed with the EQ-5D-3L and PDQ-8 indexes as dependent variables and age, sex, PD duration, SCOPA-Motor subscales (Activities of Daily Living, dyskinesias, and fluctuations), HADS-Depression, PDSS-2 total score, and KPPS total score or individual domains as explanatory variables. For phase 2, dependent variables were again EQ-5D-3L and PDQ-8 indexes, whereas the explanatory variables were age, sex, PD duration, and the KPPS domains. Normality of residuals, multicollinearity and homoscedasticity were checked and found acceptable in the four models.
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