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Posted Date: 3 June 2026

doi: 10.20944/preprints202606.0275.v1

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 doi:10.20944/preprints202606.0275.v1

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Depression and Mood Changes in People with Parkinson's Disease Over Time: A 5-Year Follow-Up Study

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Abstract

Background and objective: Depression is frequent in Parkinson's disease (PD), but it is unclear how mood changes and impacts patient's quality of life (QoL) over time. Our objective was to analyze the frequency of depression and mood changes in people with PD (PwP) over 5 years of follow-up, comparing it with a control group, as well as its relationship with the patients' QoL. **Patients and Methods:** PwP and healthy controls (HC) recruited from the COPPADIS cohort from January/2016 to November/2017 were included in this 5-year follow-up study. Mood was assessed by the Beck Depression Inventory II (BDI-II), and participants were classified as having major depression, minor

 doi:10.20944/preprints202606.0275.v1

depression, subthreshold depression, or non-depression at baseline and at 2, 4, and 5 years of follow-up. Correlation analysis and linear regression models were applied. **Results:** The BDI-II total score increased from 8.1 ± 6.2 at baseline to 10.3 ± 8.1 at the 5-year follow-up visit in PwP ($p<0.0001$) but not in HC (from 4.1 ± 5.2 to 4.0 ± 5.7 [$p=0.896$]). The prevalence of depression remained around 50–54% in the PwP group and 21–25% in the HC group throughout the follow-up period, but the mood state showed variability for each patient between visits. Patients' QoL was associated with the depressive state throughout the entire follow-up period ($p<0.0001$). Worsening QoL, sleep, longer disease duration, and an increase in neuropsychiatric symptoms were identified as independent factors associated with a worsening of mood over time in PwP (N=348). **Conclusion:** Mood changes over time in PwP and are associated with QoL.

Keywords: cohort; depression; mood; non-motor symptoms; parkinson's disease; prospective study

Introduction

Depression is one of the most frequent and disabling non-motor symptoms (NMS) in Parkinson's disease (PD), and, in some patients, it may represent the main determinant of quality of life (QoL) [1–3]. In this context, NMS constitute a major source of disability that, in many cases, may outweigh that associated with the classical motor manifestations, significantly affecting both patients and caregivers. Among them, depression stands out as one of the most relevant neuropsychiatric features, alongside anxiety, fatigue, and pain [2].

The prevalence of depression in PD shows wide variability, reaching up to 90% depending on diagnostic criteria. However, it is estimated that approximately 35–40% of patients present clinically significant depressive symptoms, while 17–20% meet criteria for major depressive disorder [2,4,5]. Moreover, its incidence is approximately twice as high as in individuals without PD and can be up to ten times higher than that observed in the general population over 50 years of age [2]. Depressive symptoms may appear throughout the entire disease course, even preceding the clinical diagnosis. In this regard, population-based studies have shown that the risk of depression may be increased up to 8–10 years before PD diagnosis, and its frequency continues to rise thereafter [6,7]. In addition, a substantial proportion of patients present subclinical depressive symptoms, which are associated with an increased risk of progression to major depression, highlighting the importance of early identification [2]. Despite its high prevalence, depression in PD remains underdiagnosed, partly due to symptom overlap with the disease itself. Manifestations such as sleep disturbances, fatigue, or cognitive slowing may be attributed either to PD or to depression, complicating recognition and delaying treatment [2,4,8]. In addition, the presence of subclinical or milder depressive symptoms further contributes to diagnostic complexity and may hinder identification in clinical practice [2,4]. From a pathophysiological perspective, depression in PD is likely to have a multifactorial origin, involving alterations in multiple neurotransmitter systems —including dopaminergic, serotonergic, and noradrenergic pathways— together with dysfunction of fronto-limbic and cortico-striatal circuits, inflammatory processes, and neuroendocrine changes [2,7].

Depression in PD has consistently been associated with a more unfavorable clinical course, including greater motor, functional, and cognitive impairment, as well as increased mortality [1,2]. It is also associated with poorer QoL across all stages of the disease [9,10]. We observed in Spanish PD patients from the COPPADIS cohort that an increase of ≥ 5 points on the Beck Depression Inventory – II (BDI-II) after 2 years of follow-up multiplied the probability of presenting clinically significant health-related QoL impairment by 5 [11]. Even having subthreshold depression has been demonstrated to be associated with a worse QoL [12].

In spite of the available evidence, the longitudinal relationship between depression and the clinical progression of PD, as well as its differential impact according to symptom severity, including subclinical forms, has not been fully characterized [1]. Therefore, the aim of this study was to analyze

 doi:10.20944/preprints202606.0275.v1

the frequency and progression of depressive symptoms in people with PD (PwP) over a five-year follow-up period, compared with a healthy control group, and to assess their relationship with QoL.

Material and Methods

This observational, prospective, population-based, multicenter study included PwP and healthy controls (HC) recruited from 35 hospital centers across Spain, all belonging to the COPPADIS cohort [13]. Participants, who were non-demented and aged between 30 and 75 years, were recruited between January 2016 and November 2017. The study design corresponds to a five-year prospective multicenter longitudinal study aimed at analyzing PD progression in a Spanish population. The full methodology of the COPPADIS-2015 study has been previously described [14].

Participants were assessed at baseline (V0) and after 2 (V2), 4 (V4), and 5-year follow-up (V5). Mood was assessed using the BDI-II [15]. Based on selected items (1, 4, 5, 9, 13, 15, 16, 17, and 18), participants were classified as follows [14]: major depression (≥ 5 symptoms including sadness [item 1] and/or anhedonia [item 4], according to DSM-IV criteria), minor depression (2–4 symptoms including item 1 and/or 4), or subthreshold depression (2–4 symptoms without items 1 or 4, according to Judd criteria) [16,17]. Participants not meeting these criteria were classified as non-depressed. QoL was assessed using three instruments: the 39-item Parkinson's disease questionnaire (PDQ-39) [18]; PQ-10 [19]; and the EUROHIS-QOL 8-item index (EUROHIS-QOL8) [20]. The PDQ-39 is a PD-specific questionnaire comprising 39 items grouped into eight domains (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort), scored from 0 (never) to 4 (always) and referring to the previous four weeks. Scores are transformed into percentages and summarized as the PDQ-39 Summary Index (PDQ-39SI). The PQ-10 assesses overall perceived quality of life on a scale from 0 (worst) to 10 (best). The EUROHIS-QOL8, derived from the WHOQOL-BREF, includes 8 items (quality of life, health, energy, autonomy, self-esteem, social relationships, financial situation, and environment), scored from 0 to 5, with higher values indicating better QoL.

Moreover, sociodemographic, clinical, comorbidity, and pharmacological treatment data were collected. The evaluation covered multiple clinical domains in addition to mood and QoL [14]: motor status (Hoehn and Yahr [H&Y], Unified Parkinson's Disease Rating Scale [UPDRS-III and UPDRS-IV], Freezing of Gait Questionnaire [FOGQ]); non-motor symptoms (Non-Motor Symptoms Scale [NMSS], Parkinson's Disease Sleep Scale [PDSS], Visual Analog Scale for Pain [VAS-Pain], Visual Analog Fatigue Scale [VAFS]); cognition (MMSE, Parkinson's Disease Cognitive Rating Scale [PD-CRS]); neuropsychiatric symptoms (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]).

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 for Windows. Only participants with complete data for BDI-II were included. Quantitative variables were expressed as mean ± standard deviation (SD) or median [p25, p75], depending on their distribution. Categorical variables were expressed as frequencies and percentages. Normality was assessed using the Kolmogorov–Smirnov test. Group comparisons (major depression vs. minor depression vs. subthreshold depression vs. non-depression) were performed using the chi-square test or analysis of variance (ANOVA), as appropriate. Correlations between the change in mood (BDI-II score) from V0 to V5 and the change in other continuous PD-related variables from V0 to V5 in PwP were analyzed using Pearson or Spearman correlation coefficients, depending on data distribution. Correlations were interpreted as weak (≤0.29), moderate (0.30–0.59), or strong (≥0.60).

To analyze factors associated with mood change, a multiple linear regression model was constructed using the change in BDI-II score from V0 to V5 (ΔBDI-II) as the dependent variable. Univariate analyses were first performed, and variables showing significant associations were included in the multivariate model. Following methodological recommendations, clinically relevant

 doi:10.20944/preprints202606.0275.v1

covariates were included: age, sex, disease duration, the change from V0 to V5 in the UPDRS-III (OFF), UPDRS-IV, FOGQ, PD-CRS, NMSS, PDSS, NPI, VAS-Pain, VASF-physical, VASF-mental, PDQ-39SI, EUROHIS-QOL8, and ADLS, and to be taking at V5 antidepressants, benzodiazepines, and antipsychotics. Model fit was assessed using the adjusted coefficient of determination (adjusted R^2), and residual independence using the Durbin–Watson statistic. Results were expressed as β coefficients, 95% confidence intervals, and p-values.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by local and national research ethics committees in accordance with current regulations. All participants provided written informed consent prior to inclusion. The COPPADIS-2015 project was classified by the Spanish Agency of Medicines and Medical Devices (AEMPS) as a prospective post-authorization follow-up study (code: COH-PAK-2014-01).

Data Availability

The protocol and the statistical analysis plan are available on request. De-identified participant data are not available for legal and ethical reasons.

Results

A total of 692 PwP (62.6 ± 8.9 years old, 60.4% males) and 207 HC (61 ± 8.3 years old, 49.5% males) with complete data for BDI-II were recruited at baseline. In all visits (V0, V2, V4 and V5), the mean BDI-II score was significantly higher in the PwP group than in the HC group ($p<0.0001$ for all visits) (**Figure 1**). The BDI-II total score increased from 8.1 ± 6.2 at baseline (V0) to 10.3 ± 8.1 at the 5-year follow-up visit (V5) in PwP ($p<0.0001$) but not in HC (from 4.1 ± 5.2 to 4.0 ± 5.7 [$p=0.896$]) (**Figure 1**). Depression (i.e., to have major depression, minor depression, or subthreshold depression) was significantly more frequent in PwP compared with HC at baseline (V0) and in all follow-up visits (V2, V4 and V5) ($p<0.0001$ for all visits) (**Figures 2A** and **2B**). Specifically, the prevalence of depression remained around 50–54% in the PwP group and 21–25% in the HC group throughout the follow-up period (**Figure 2B**).

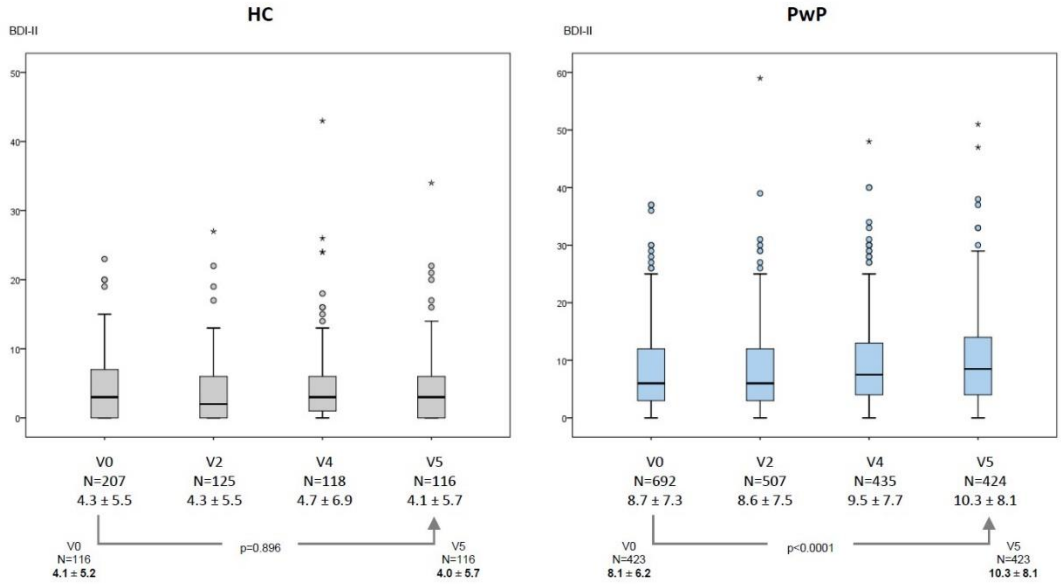

Figure 1. BDI-II score at each visit throughout follow-up (V0, V2, V4, and V5) in PwP and HC from the COPPADIS cohort. Non-parametric tests were applied to analyze the change from V0 to V5 in the BDI-II score in both PwP and HC. HC, healthy controls; PwP, people with Parkinson's disease.

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At the individual level, longitudinal trajectory analysis in PwP (N = 346; PwP with data for mood stage classification in all visits) revealed marked variability in mood states, with frequent transitions between depression categories over time (**Figure 2C**). Only 17.1% of patients remained consistently non-depressed, while 34.4% of initially non-depressed individuals developed incident depression. Sustained remission was observed in only 8.4% of patients. Persistent depression was identified in 19.1%, whereas 18.2% exhibited a true relapse pattern following remission. Additionally, 9.5% showed a fluctuating course. Overall, 74.5% of the PwP cohort experienced depression at some point during follow-up (**Figure 2C**).

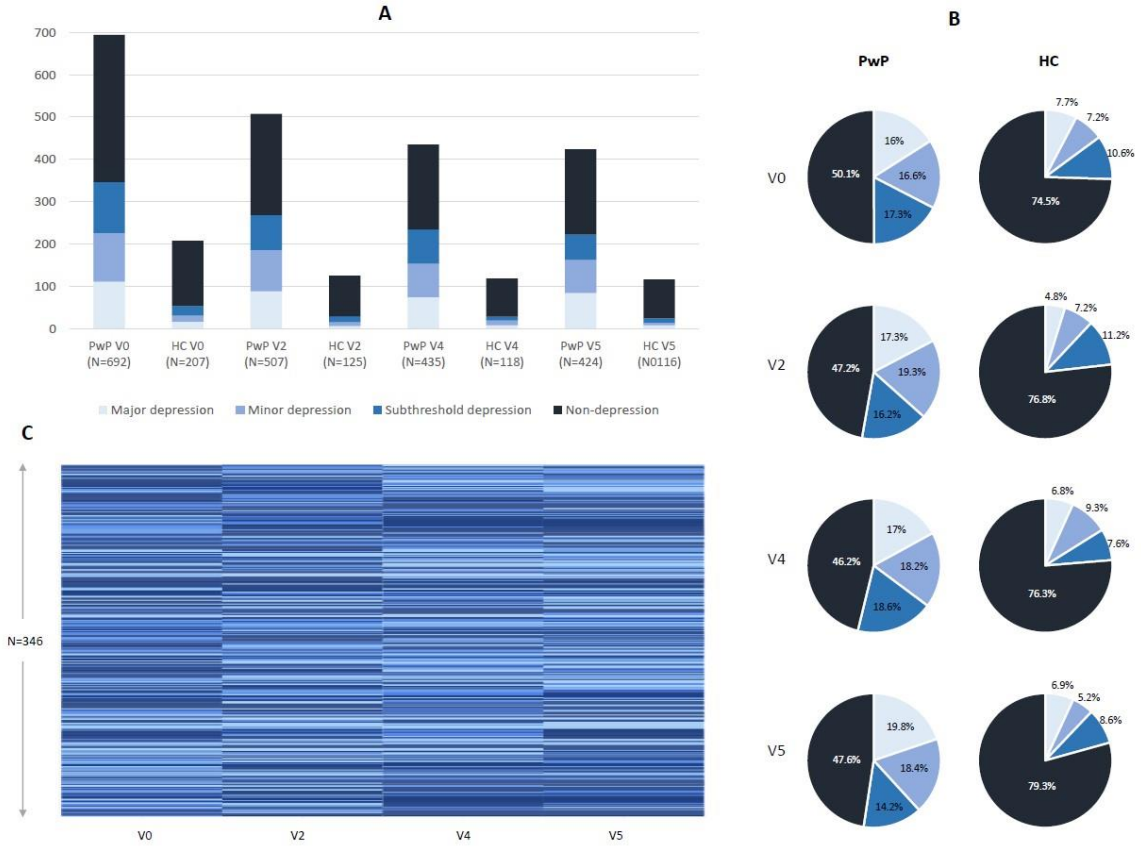

Figure 2. Number (N) of PwP and HC (**A**) and frequency (%) of PwP and HC (**B**) with major depression, minor depression, subthreshold depression, and non-depression at baseline (V0), 2-year (V2), 4-year (V4), and 5-year (V5) follow-up visits. **C.** Mood state for each patient from the PwP group at each visit. HC, healthy controls; PwP, people with Parkinson's disease.

At baseline, PwP with major depression exhibited a more severe motor affectation compared to other groups (**Table 1**). Specifically, they showed a higher score on the UPDRS-IV (p=0.006) and FOGQ (p<0.0001) along with a higher frequency of motor fluctuations (p=0.040) compared to PwP with minor depression and subthreshold depression (**Table 1**). Regarding NMS, the NMS score was significantly higher in PwP with major depression (92.4 ± 51.4) compared to minor (56.2 ± 33.9), subthreshold (47.0 ± 32.3), and non-depressed PD patients (28.4 ± 24.7) (p<0.0001). Similarly, cognitive performance was worse in PwP with major depression compared to the other groups, with a lower PD-CRS total score (86.3 ± 14.7 vs. 87.7 ± 14.0 vs. 94.3 ± 16.0 vs. 94.5 ± 14.5; p<0.0001), and including the fronto-subcortical (p=0.002) score (**Table 1**). Neuropsychiatric symptoms (NPI), impulse control disorder (QUIP-RS), sleep quality (PDSS), pain (VAS-PAIN), and fatigue (VASF – physical and VASF – mental) followed the same pattern, with scores showing the greatest affectation in PwP with major depression and the lowest in those PwP with non-depression (**Table 1**; p<0.0001 for all analyses).

 doi:10.20944/preprints202606.0275.v1

Table 1. Motor and non-motor symptoms, autonomy for activities of daily living, quality of life and other aspects related to PD in PwP at baseline (V0) according to mood state (N=346).

	All cohort (N=346)	Major depression (N=46)	Minor depression (N=62)	Subthreshold depression (N=60)	Non depression (N=178)	p
Age	62.0 ± 8.7	61.5 ± 8.6	63.3 ± 7.9	62.7 ± 9.2	62.2 ± 8.7	
Sex (males) (%)	57.7	39.1	54.8	61.7	62.1	0.399
Disease duration	5.4 ± 4.3	5.8 ± 4.6	4.7 ± 3.6	5.6 ± 5.2	5.4 ± 4.1	**0.036**
LEDD	545.3 ± 378.7	520.2 ± 370.1	522.4 ± 373.1	590.6 ± 348.3	544.5 ± 394.1	0.507
Motor phenotype (%):	49.7	39.1	51.6	53.3	50.6	0.733
- Tremor-dominant	32.7	43.5	35.5	38.3	27	0.074
- PIGD	17.6	17.4	12.9	8.4	22.4	**0.007**
- Indeterminate	2 [2,2]	2 [2,2.5]	2 [2,2]	2 [2,2]	2 [1.5,2]	0.097
Hoehn & Yahr - OFF	7.4	18.2	8.2	6.9	4.3	0.206
- Stage from 3 to 5 (%)	21.9 ± 10.3	24.6 ± 9.9	21.6 ± 10.7	22.7 ± 10.9	21.0 ± 9.9	**0.006**
UPDRS-III - OFF	1.9 ± 2.3	2.8 ± 2.2	2.2 ± 2.3	1.9 ± 2.3	1.6 ± 2.2	**0.040**
UPDRS-IV	33.5	50	37.1	33.3	28.1	**<0.0001**
- Motor fluctuations (%)	3.6 ± 4.4	5.8 ± 4.4	3.9 ± 4.8	3.9 ± 4.4	2.8 ± 4.1	**<0.0001**
FOGQ	92.2 ± 15.1	86.3 ± 14.7	87.7 ± 14.0	94.3 ± 16.0	94.5 ± 14.5	**0.002**
PD-CRS	64.4 ± 13.8	59.3 ± 14.0	60.8 ± 12.4	66.3 ± 14.7	66.4 ± 13.4	**0.023**
- FS sub-score	27.8 ± 3.3	27.0 ± 3.7	26.9 ± 4.4	28.1 ± 2.9	28.2 ± 2.8	**<0.0001**
- PC subscore	45.2 ± 38.8	92.4 ± 51.4	56.2 ± 33.9	47.0 ± 32.3	28.4 ± 24.7	**<0.0001**
NMSS	8.2 ± 7.1	18.4 ± 6.9	11.5 ± 6.4	8.7 ± 4.5	3.6 ± 4.4	**<0.0001**
BDI-II	5.8 ± 8.1	15.2 ± 12.1	7.8 ± 6.9	5.8 ± 6.8	2.6 ± 4.9	**<0.0001**
NPI*	3.9 ± 7.8	5.5 ± 8.1	3.6 ± 6.9	7.6 ± 10.5	2.6 ± 4.9	**<0.0001**
QUIP-RS	117.3 ± 24.6	100.2 ± 27.1	115.3 ± 19.4	119.3 ± 19.5	122.1 ± 25.1	**<0.0001**
PDSS	2.7 ± 2.9	4.3 ± 2.7	3.3 ± 3.3	2.7 ± 2.9	2.1 ± 2.8	**<0.0001**
VAS-PAIN	2.9 ± 2.7	5.3 ± 2.6	3.1 ± 2.6	3.6 ± 2.8	1.9 ± 2.3	**<0.0001**
VASF – physical	2.1 ± 2.5	4.6 ± 2.8	2.3 ± 2.4	2.3 ± 2.7	1.3 ± 2.0	**<0.0001**
VASF – mental	88.9 ± 10.1	83.3 ± 13.0	88.9 ± 10.1	88.7 ± 8.7	91.5 ± 8.5	**<0.0001**
ADLS	16.5 ± 13.2	28.9 ± 13.1	19.7 ± 12.2	19.3 ± 13.1	11.3 ± 10.4	**<0.0001**
PDQ-39SI	3.8 ± 0.5	3.4 ± 0.6	3.5 ± 0.5	3.7 ± 0.5	4.0 ± 4.4	**<0.0001**
EUROHIS-QOL8	7.3 ± 1.6	6.1 ± 1.9	6.7 ± 1.5	7.3 ± 1.5	7.7 ± 1.3	0.286
PQ-10	68.8	80.4	64.5	70	66.9	0.067
Treatments (%):	71.4	58.7	64.5	75	75.8	**0.047**
- Levodopa	75.4	65.2	66.1	80	79.8	0.546
- Dopamine agonist	18.8	16.9	19.4	20	18	0.724
- MAO-B inhibitor	7.5	6.5	4.8	6.7	9	**<0.0001**
- COMT inhibitor	23.1	50	35.5	20	12.9	**<0.0001**
- Amantadine	15.9	39.1	17.7	11.7	10.7	0.734
- Antidepressant	1.2	2.2	0	1.7	1.1	**0.003**
- Benzodiazepine	25.7	43.5	33.9	18.3	20.8	
- Antipsychotic						
- Analgesics						

The results represent percentages, mean ± SD or median [p25, p75]. Chi-squared and ANOVA tests (p value) were applied to compare between groups. Data about H&Y and UPDRS-III are during the

 doi:10.20944/preprints202606.0275.v1

OFF state (first thing in the morning without taking medication in the previous 12 hours). Motor phenotype, motor fluctuations, FOG, and falls were defined in the COPPADIS protocol according to the literature and scales used (reference 14).*Data represents the total score of the NPI (sum from domain A to J) informing about the subject (caregiver distress is not shown). Not all information was collected for all variables, varying the range from 346 (most variables) to 290 (NPI). ADLS, Schwab and England Activities of daily living Scale); BDI-II, Beck Depression Inventory-II; FOGQ, Freezing of Gait Questionnaire; FOG, freezing of gait; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; PDSS, Parkinson's Disease Sleep Scale; PIGD, Postural Instability Gait Difficulty; 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.

According to the BDI-II total score, worsening depressive symptoms correlated with impairment in motor severity (UPDRS-III OFF; r=0.186; p=0.001), motor complications (UPDRS-IV; r=0.104; p=0.008), and freezing of gait (FOGQ; r=0.222; p<0.0001) (**Table 2**). Stronger associations were observed with an increase of NMS burden (NMSS, r=0.460; p<0.0001), neuropsychiatric symptoms (NPI; r=0.461; p<0.0001), physical (VASF–physical; r=0.273; p<0.0001) and mental fatigue (VASF–mental; r=0.299; p<0.0001), cognitive decline (PD-CRS; r=−0.240; p<0.0001), and sleep impairment (PDSS; r=−0.274; p<0.0001). Regarding QoL (PDQ-39SI; PQ-10; EUROHIS-QOL8) and disability (ADLS) at baseline, the scales again showed a worse QoL and less autonomy for activities of daily living in patients with major depression, with a pattern of less impairment the fewer depressive symptoms were present, with those without depression being the least affected (**Table 1**). These findings were similarly observed for health-related (PDQ-39SI) and global (PQ-10; EUROHIS-QOL8) QoL across all follow-up visits, with significant differences between groups in all analyses (p<0.0001 for all analysis) (**Figure 3**).

Table 2. Correlation between the change in mood (BDI-II score) from V0 to V5 and the change in other PD-related variables from V0 to V5 in PwP (N=346). .

Change from V0 to V5	Change at V5 (V5 – V0) (N=346)	Correlation with change in mood (BDI-II) at V5 (V5-V0)	p
LEDD (mg/day)	+320.1 ± 422.3	-0.033	0.537
UPDRS-III (OFF)	+9.2 ± 14.4	0.186	**0.001**
UPDRS-IV	+1.7 ± 3.1	0.104	**0.008**
FOGQ	+2.8 ± 4.9	0.222	**<0.0001**
PD-CRS	-4.5 ± 17.2	-0.240	**<0.0001**
NMSS	+14.0 ± 40.4	0.460	**<0.0001**
BDI-II	+2.0 ± 7.3	N. A.	N.A.
PDSS	-0.6 ± 26.8	-0.274	**<0.0001**
QUIP-RS	-0.1 ± 9.5	-0.001	0.985
NPI	+3.2 ± 10.6	0.461	**<0.0001**
VAS-PAIN	+0.9 ± 3.5	0.095	0.079
VASF – physical	+1.1 ± 3.3	0.273	**<0.0001**
VASF – mental	+0.7 ± 3.4	0.299	**<0.0001**
PDQ-39SI	+7.2 ± 14.1	0.572	**<0.0001**
EUROHIS-QOL8	-1.6 ± 4.3	-0.491	**<0.0001**
PQ-10	0.4 ± 1.7	-0.246	**<0.0001**
ADLS	-10.3 ± 15.8	-0.375	**<0.0001**

Spearman's or Pearson rank correlation coefficient was applied. In bold, p<0.05. ADLS, Schwab & England Activities of Daily Living Scale; BDI-II, Beck Depression Inventory-II; FOGQ, Freezing Of

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Gait Questionnaire; LEDD, levodopa equivalent daily dose; N. A. , not applicable; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD-CRS, Parkinson's Disease Cognitive Rating Scale; 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.

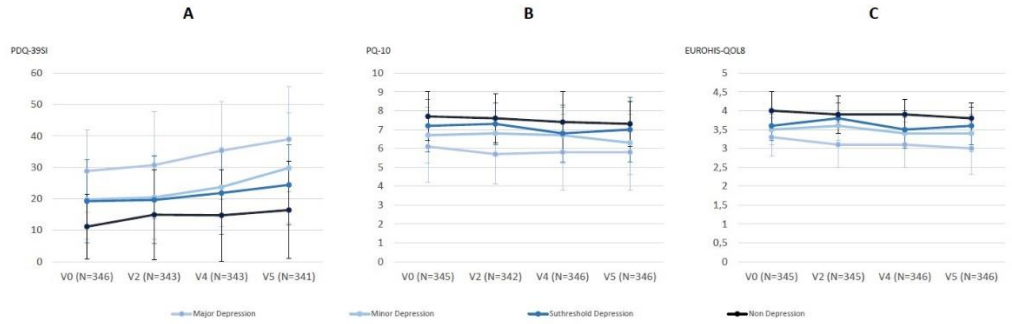

Figure 3. Mean and standard deviation on PDQ-39SI (**A**), PQ-10 (**B**), and EUROHIS-QOL 8 (**C**) at baseline (V0), 2-year (V2), 4-year (V4), and 5-year (V5) follow-up visits in PwP. The ANOVA test was used for comparison between all groups (major depression vs. minor depression vs. subthreshold depression vs. non-depression); p<0.0001 for all analyses (A, B, and C). EUROHIS-QOL8, EUROHIS-QOL 8-item index; PDQ-39SI, Parkinson's Disease Questionnaire - 39 item Summary Index.

Multivariate analysis identified several factors significantly associated with changes in depressive symptoms over 5 years in PwP (**Table 3**). Specifically, the change from V0 to V5 in the EUROHIS-QOL8 (r=−0.240; p=0.001), NPI (r=0.233; p=0.001), PDSS (r=-0.187; p=0.001), PDQ-39SI (r=0.164; p=0.036), and disease duration (r=0.115; p=0.041) were identified as independent factors associated with the change in the BDI-II from V0 to V5 after adjustment to covariates (**Table 3**). The multivariate model explained 44% of the variance in changes in depressive symptoms over 5 years (adjusted R^2=0.44).

Table 3. Factors associated with mood (BDI-II score) change from baseline (V0) to the 5-year follow-up visit (V5) ($BDI\text{-}II_{V5}$ – $BDI\text{-}II_{V0}$) in PD patients (N=346).

	β[a]	95% CI[a]	p	Durbin – Watson test	Adjusted R^2	β[b]	95% CI[b]	p[b]
Change in the EUROHIS-QOL8	-0.491	-0.99 - -0.68	<0.0001	2.19	0.44	-0.240	-0.62 - -0.17	0.001
Change in the NPI	0.461	0.25 – 0.39	<0.0001			0.233	0.07 – 0.25	0.001
Change in the PDSS	-0.274	-0.10 - -0.05	<0.0001			-0.187	-0.09 - -0.02	0.001
Change in the PDQ-39SI	0.572	0.25 – 0.34	<0.0001			0.164	0.01 – 0.17	0.036
Disease duration	0.092	-0.03 – 0.35	0.096			0.115	0.01 – 10.38	0.041

Dependent variable: Change from V0 to V5 in the BDI-II total score. The β coefficient and 95% IC are shown. a, univariate analysis; b, multivariate analysis. Only data of variables significant in the multivariate analysis is shown. Factor included as covariates were age, sex, disease duration, the change from V0 to V5 in the UPDRS-III (OFF), UPDRS-IV, FOGQ, PD-CRS, NMSS, PDSS, NPI, VASF – physical, VASF – mental, PDQ-39SI, EUROHIS-QOL8 and S&E-ADLS, and to be taking at V5 antidepressants, benzodiazepines and antipsychotics. ADLS, Schwab & England Activities of Daily Living Scale; BDI-II, Beck Depression Inventory-II; FOGQ, Freezing Of Gait Questionnaire; NMSS,

 doi:10.20944/preprints202606.0275.v1

Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDSS, Parkinson's Disease Sleep Scale; UPDRS, Unified Parkinson's Disease Rating Scale; VAFS, Visual Analog Fatigue Scale; VAS-Pain, Visual Analog Scale-Pain.

Discussion

Our results showed that depressive symptoms are significantly more frequent in PwP than in HC and, additionally, tend to progress over time. In our cohort, approximately 50% of patients presented some form of depressive symptoms, with major depression between 17% and 19% throughout the 5-year follow-up. Importantly, the presence of depression in our study was significantly associated with greater clinical severity and functional impairment from baseline to the end of follow-up, highlighting its broad impact on disease progression.

The frequency of depression in our study coincides with what has been previously reported in the literature. Large meta-analyses and reviews report depressive disorders in about 30–40% of PwP, with major depressive disorder in about 14–19% [21,22]. When broader definitions or symptom scales are used, clinically significant depressive symptoms are seen in roughly 35–46% of patients [23,24]. Detecting the presence of depressive symptoms in PwP is important not only because it is common but also because its presence is associated with a worse clinical state. In our cohort, mood status was associated with the degree of clinical involvement in motor symptoms and NMS, as well as in QoL and disability, with PwP with major depression being the most affected and, at the other extreme, those without depression being the least affected. Across cross-sectional and longitudinal studies, depression in PD is clearly associated with more severe motor disease, higher disability, poorer QoL, and less favorable cognitive and survival [2,25–31]. Specifically, depressed PD patients have longer disease duration, higher motor scores (UPDRS-III), a higher H&Y stage, and lower activities of daily living scores than non-depressed patients [26,29]. Notably, patients with minor and subthreshold depression already exhibited a worse clinical profile compared to non-depressed individuals, suggesting that the association between depression and clinical impairment is present even at subclinical stages [12]. Consistent with this observation, previous studies have shown that even mild depressive symptoms may be associated with gait disturbances in early PD, reinforcing the clinical relevance of depressive symptoms across their full severity spectrum [32].

Regarding the NMS, patients with major depression showed a significantly higher burden, approximately three times greater than those without depression, while the minor and subthreshold groups displayed intermediate values. This is also conditioned by the fact that depressive symptoms are an aspect that is included in the evaluation (i.e., NMSS), and also because a more depressive mood can influence the perception of symptoms in general, including NMS as a whole or specific NMS such as pain or fatigue, as more disabling. Similarly, the burden of neuropsychiatric symptoms followed a comparable pattern, with a progressive increase according to depression severity, further supporting a close relationship between depression and overall neuropsychiatric burden. Previous studies found greater depressive severity in PD patients with pain [2,33] like in our cohort. Chronic pain may contribute to sleep disturbances, promoting fragmentation and reducing sleep quality [34]. In PD, this interaction is particularly relevant due to degeneration of the systems involved in the sleep–wake cycle, including noradrenergic, serotonergic, dopaminergic, and GABAergic pathways, contributing to the high prevalence of sleep disorders [34,35]. Accordingly, greater depressive severity was associated with poorer sleep quality, in line with evidence linking reduced sleep efficiency to neurobiological alterations and cognitive dysfunction, as we found, possibly mediated by changes in fronto-visual connectivity [36]. This relationship may reflect a bidirectional interaction between sleep and depression, partly mediated by GABAergic dysfunction and hyperactivation of the hypothalamic–pituitary–adrenal axis, forming a cycle of clinical deterioration [34,36,37].

In the present study, we observed how the change in mood in the long-term correlated with the worsening in many aspects of the disease, including both motor symptoms and NMS. In a large clinic cohort (N=1214), Camerucci et al. observed that increasing depression severity was associated with worsening motor symptoms (UPDRS, H&Y), NMS, sleepiness, and poorer cognition [31].

 doi:10.20944/preprints202606.0275.v1

Furthermore, depression is associated with greater disease progression and disability [28,38]. Regarding QoL, multiple studies and reviews identify depression as the primary driver of reduced QoL, often more impactful than motor severity itself [2,39–42]. In our study, worsening mood over the course of the disease was independently associated with longer disease duration and worsening sleep quality and an increase in neuropsychiatric symptoms, but also with a greater deterioration in global and health-related QoL. Understanding the patient's mood is key, since in each follow-up visit it was associated with QoL; the greater the severity of depressive symptoms, the worse the QoL.

From a pathophysiological perspective, depression in PD can be understood as the result of a multifactorial model in which neurobiological mechanisms, clinical factors, and psychosocial elements interact [7] and as a manifestation of both the psychological response to the disease and the underlying neurodegenerative process itself [7,43]. Our findings align with this model, as greater overall impairment was associated with more severe depression, poorer QoL, and greater difficulties in activities of daily living, with these differences persisting throughout follow-up. Despite therapeutic advances, remission rates in depression remain limited, with approximately 30% of patients not responding to treatment and high relapse rates [44]. Although previous studies estimate that 40–50% of patients with PD experience depressive symptoms during the disease course [45], our cohort showed a higher burden, with nearly 75% affected at some point during follow-up. Longitudinal analysis revealed that sustained remission was uncommon. Instead, 18.2% of patients exhibited a pattern of true relapse, while 19.1% showed persistent depression throughout follow-up, highlighting the recurrent and heterogeneous nature of depressive trajectories in PD.

The present study has some limitations. First, although it is a large, multicenter cohort with a five-year longitudinal follow-up, the observational nature of the design precludes establishing causal relationships between depression and the clinical progression of PD, limiting conclusions to associations. Second, depressive symptoms were assessed using clinical rating scales (BDI-II) rather than structured diagnostic interviews, which may introduce some heterogeneity in the classification of depression subtypes (major, minor, and subthreshold), as well as potential overlap with somatic symptoms inherent to PD. Furthermore, although multiple clinical variables were included and multivariate analyses were performed, the influence of unmeasured confounding factors cannot be excluded. These include social variables, specific psychopharmacological treatments, or therapeutic changes over time, all of which may have influenced the course of depressive symptoms. In addition, the potential loss of participants during follow-up and variability in sample size across visits may have introduced a degree of selection bias, potentially favoring patients with better clinical follow-up. Finally, although the study includes a comprehensive assessment of multiple clinical domains, some relevant constructs —such as anxiety and apathy— were not specifically analyzed in all models, which may limit a comprehensive characterization of the neuropsychiatric spectrum in Parkinson's disease.

Overall, this study shows that depressive symptoms are highly prevalent in PD and follow a dynamic longitudinal pattern over time, characterized by an overall tendency toward worsening and marked inter-individual variability. Depression is consistently associated with a worse global clinical profile, including greater motor and non-motor severity, cognitive impairment, sleep disturbances, higher neuropsychiatric burden, poorer QoL, and increased functional dependency. This effect follows a gradient according to depressive severity and is already evident even in subclinical forms. Beyond this, the evolution of depressive symptoms appears to be modulated by multiple interrelated factors, such as QoL, sleep disturbances, and neuropsychiatric burden, reflecting a complex interaction between motor and non-motor domains. Taken together, these findings highlight the importance of early detection of depression in PD, even at mild or subclinical stages, as well as the need for a comprehensive and multidisciplinary clinical approach that integrates mental health assessment into routine neurological care, with the aim of optimizing overall disease progression and patients' QoL.

 doi:10.20944/preprints202606.0275.v1

Author Contributions: Ángela Solleiro Vidal: writing of the first draft of the manuscript. Diego Santos-García: conception, organization, and execution of the project; statistical analysis; writing of the first draft of the manuscript together with Ángela Solleiro Vidal. Rest of the authors: review and critique; recruitment and/or evaluation of participants and/or data entry into eCRF.

Funding: The Fundación Degen is the promoter of the project COPPADIS study. This project is being carried out using resources obtained by the Fundación Degen in collaboration with the Sociedad Española de Neurología and the Grupo de Estudio de Trastornos del Movimiento (GETM) of the Sociedad Española de Neurología.

Institutional Review Board Statement: The study was conducted in accordance with the ICH Good Clinical Practice version 6 Revision 2 standard, the fundamental ethical principles established in the Declaration of Helsinki and the Oviedo Convention, as well as the Spanish legal requirements for biomedical research (Biomedical Research Law 14/2007). The study was approved on 02/APR/2024 by the IRB "Comité de Ética de la Investigación Clínica de Galicia from Spain" with code number COH-PAK-2014-01).

Informed Consent Statement: Written informed consent from all participants (patients and controls) in this study was obtained.

Data Availability Statement: The protocol, statistical analysis plan and unidentified participant data will be available on request.

Acknowledgments: We would like to thank all patients and their caregivers who collaborated in this study. Thanks to Fundación Degen and Sociedad Española de Neurología.

Conflicts of interest: Ángella **Solleiro Vidal** has nothing to report. Diego **Santos García** has received honoraria for educational presentations and advice service by Abbvie, KRKA, Zambon, Bial, Italfarmaco, Teva, Archímedes, Brittania, Merz, Esteve, Stada, Orion Pharma, financial compensation for INIBIC/Fundación Professor Novoa Santos in relation to activity as PI in phase 2 to phase 4 clinical trials for Parkinson's disease and other movement disorders, compensation for Fundación Degen in relation to different projects, and grants from the "Fundación Professor Novoa Santos" as a result of the "CONVOCATORIA DE AYUDAS PARA LA REALIZACIÓN DE PROYECTOS DE INVESTIGACIÓN PARA GRUPOS EMERGENTES Y ASOCIADOS DEL INIBIC (2023/2024)". Alfredo **Puy Núñez** has received honoraria from Almirall, Biogen, Ferrer, Krka, Merck, Novartis, Nutricia, Roche and UCB and sponsorship from Abbvie, Almirall, Alter, Bial, Biogen, Eisai, Krka, Lundbeck, Merck, Neuraxpharm, Novartis, Roche, UCB and Zambon for attending medical conferences. Teresa **de Deus Fonticoba** has nothing to report. Pablo **Mir** has received financial support from the Spanish Ministry of Science and Innovation (RTC2019-007150-1), the Instituto de Salud Carlos III-Fondo Europeo de Desarrollo Regional (ISCIII-FEDER) (PI16/01575, PI18/01898, PI19/01576, PI20/00613, PI21/01875, PI22/01704, PI23/00512), the Consejería de Economía, Innovación, Ciencia y Empleo de la Junta de Andalucía (CVI-02526, CTS-7685), the Consejería de Salud y Bienestar Social de la Junta de Andalucía (PI-0471-2013, PE-0210-2018, PI-0459-2018, PE-0186-2019), the Consejería de Transformación Económica, Industria, Conocimiento y Universidades de la Junta de Andalucía (PY20_00896), and support for attending meetings and/or travel or honorarium for lecturing from Abbott, Allergan, Abbvie, Bial, Britannia, Italfarmaco, Merz, UCB, Teva and Zambon. Gracia **Pons Pons** has nothing to report. Juan **García Caldentey** has received honoraria for educational presentations and advice service by Qualigen, Nutricia, Abbvie, Italfarmaco, UCB Pharma, Lundbeck, Zambon, Bial, and Teva. Nuria **Caballol** has received honoraria from Bial, Italfármaco, Qualigen, Zambon, UCB, Teva and KRKA and sponsorship from Zambon, TEVA and Abbvie for attending medical conferences. Jorge **Hernández Vara** has received travel bursaries and educational grants from Abbvie and has received honoraria for educational presentations from Abbvie, Teva, Bial, Zambon, Italfarmaco, and Sanofi-Genzyme. Lydia **López Manzanares** compensated advisory services, consulting, research grant support, or speaker honoraria: AbbVie, Acorda, Bial, Intec Pharma, Italfarmaco, Pfizer, Roche, Teva, UCB, and Zambon. Bárbara **Vives Pastor** has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, and Teva. Maria A. **Ávila Rivera** has received honoraria from Zambon, UCB Pharma, Qualigen, Bial, and Teva, and sponsorship from Zambon and Teva for attending conferences. Isabel **González Aramburu** has nothing to report. Rocío **García-Ramos** has received honoraria and grants for lecturing, advisory services from Abbvie, Zambón, Bial,

 doi:10.20944/preprints202606.0275.v1

Merk, and Stada. Carmen **Borrué has nothing to report.** Julio **Dotor García-Soto** compensated advisory services, consulting, research grant support, or speaker honoraria by Merck, Sanofi-Genzyme, Allergan, Biogen, Roche, UCB and Novartis. María **Álvarez Sauco** has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, Teva, Stada, and Orphalan. Iria **Cabo** has received honoraria for educational presentations and advice service by Abbvie, Zambon, Bial, Orion, Italfarmaco, and Esteve. Guillermo **González Ortega** has received honoraria for educational purposes from ABBIE, Zambon, Bial, Esteve and Italfarmaco.

Abbreviations

ADLS, Schwab and England Activities of daily living Scale); BDI-II, Beck Depression Inventory-II; FOGQ, Freezing of Gait Questionnaire; FOG, freezing of gait; NMS, son-motor symptoms; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; PDSS, Parkinson's Disease Sleep Scale; PIGD, Postural Instability Gait Difficulty; PwP, people with Parkinson's disease; 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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 doi:10.20944/preprints202606.0275.v1

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 doi:10.20944/preprints202606.0275.v1

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 doi:10.20944/preprints202606.0275.v1

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 doi:10.20944/preprints202606.0275.v1

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 doi:10.20944/preprints202606.0275.v1

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 doi:10.20944/preprints202606.0275.v1

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 doi:10.20944/preprints202606.0275.v1

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