ORIGINAL ARTICLE

COPPADIS-2015 (COhort of Patients with PArkinson's DIsease in Spain, 2015): an ongoing global Parkinson's disease project about disease progression with more than 1000 subjects included. Results from the baseline evaluation

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Background and purpose: In Parkinson's disease (PD), the course of the disorder is highly variable between patients. Well-designed, prospective studies for identifying PD progression biomarkers are necessary. Our aim was to show the results of baseline evaluations of an ongoing global PD project, COPPADIS-2015 (COhort of Patients with PArkinson's DIsease in Spain, 2015).
Methods: This was an observational, descriptive, nationwide study (Spain). The recruitment period ended in October 2017. Baseline evaluation included more than 15 validated scales and complementary studies in a subgroup of participants.
Results: In total, 1174 subjects from 35 centres were considered valid for baseline analysis: 694 patients (62.6 ± 8.9 years old, 60.3% males), 273 caregivers (58.5 ± 11.9 years old, 31.8% males) and 207 controls (61 ± 8.3 years old, 49.5% males). The mean disease duration was 5.5 ± 4.4 years. Hoehn and Yahr stage was 1 or 2 in 90.7% of the patients whilst 33.9% and 18.1% of them presented motor fluctuations and dyskinesias, respectively. The mean Non-Motor Symptoms Scale total score was 45.4 ± 38.1, and 30.4% of the

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patients presented cognitive impairment, 16.1% major depression, 12.7% impulse control disorder, 7.2% compulsive behaviour, 57.2% pain and 13.2% falls. Compared to the control group, PD patients presented a significantly higher burden of non-motor symptoms and a worse quality of life. More than 300 subjects conducted complementary studies (serum biomarkers, genetic and neuroimaging).

Conclusions: Parkinson's disease is a complex disorder and different non-motor symptoms are frequently present and are more prevalent than in controls. In real clinical practice it is important to ask for them.

Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's disease, is a progressive disorder causing motor and non-motor symptoms that result in disability, loss of patient autonomy and caregiver burden [1]. The understanding of PD has changed over recent years. The disease is currently considered a neurodegenerative disease involving a diversity of pathways and neurotransmitters. This complexity may explain, in part, the large range of symptoms that patients may have. PD is not only a motor disorder as it also involves various non-motor symptoms that are important for different reasons [2]. Non-motor symptoms are frequent, disabling and negatively impact the patient's quality of life (QoL) and also contribute to higher caregiver distress and burden [3]. However, motor and non-motor symptom progression differs between patients. Different motor and non-motor phenotypes have been proposed [4,5]. In fact, PD has been suggested to be a complex syndrome instead of a disease [6]. Reliable and well-validated biomarkers for monitoring PD progression (motor and non-motor symptoms) are necessary and would dramatically accelerate research into both the causes for the development of different complications and the treatment of them.

COPPADIS-2015 (Cohort of Patients with Parkinson's Disease in Spain, 2015) is an ongoing global – clinical evaluations, serum biomarkers, genetic studies and neuroimaging – prospective, multicentre, non-interventional, long-term study on PD progression [7]. The objective of this project is to present a detailed study on a population of PD patients, representative of different areas of Spain, compared to a control group and to follow them up for 5 years. The study aims to identify predictors of the development of different complications and define different PD phenotypes with diverse outcomes. More than 1000 participants from 35 centres of Spain were included between January 2016 and October 2017. Here, general data about the recruitment process and the baseline evaluation, including different aspects of motor and non-motor symptoms, QoL and caregiver status, are given.

Methods

The methodology involved in COPPADIS-2015 has been published previously [7]. Figure S1 shows the information about baseline evaluations and the methodology of the study can be consulted at https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-016-0548-9 [7].

Standard protocol approvals, registrations and patient consents

For this study, approval was received from the appropriate local and national ethical standards committees. Written informed consents from all participants in this study were obtained before the start of the study. COPPADIS-2015 was classified by the AEMPS (Agencia Española del Medicamento y Productos Sanitarios) as a post-authorization prospective follow-up study with the code COH-PAK-2014-01.

Statistical analysis

Data were processed using IBM SPSS (San Francisco, CA) Stastistics 20.0 for Windows. Different variables were expressed as quantitative and/or qualitative variables. For comparisons between patients and controls, Student's t test, the Mann–Whitney U test, chi-squared test or Fisher test, as appropriate, was used (the distribution of variables was verified by the one-sample Kolmogorov–Smirnov test). Spearman's or Pearson's correlation coefficient, as appropriate, was used for analysing the relationship between continuous variables. The value of P was considered significant when it was <0.05.

Results

Initially, 45 centres from Spain were going to participate in the present study; however, nine centres (20%) dropped out. From January 2016 to October 2017,

1232 subjects (715 PD patients, 304 caregivers and 213 controls) were recruited from 36 centres. Of these subjects, 21 patients, 31 caregivers and six controls were excluded for different reasons (Fig. 1). Finally, 1174 subjects from 35 centres were considered valid for baseline analysis and are currently being followed according to the study protocol: 694 patients (62.6 ± 8.9 years old, 60.3% males), 273 caregivers (58.5 ± 11.9 years old, 31.8% males) and 207 controls (61 ± 8.3 years old, 49.5% males). With regard to the initially proposed cohort sizes [7], the percentage of recruited patients, caregivers and controls were 87% (694/800), 46% (273/600) and 52% (207/400), respectively.

Data about sociodemographic aspects, comorbidities, drugs and other therapies, and motor and non-motor symptoms are shown in Tables 1–3. The mean disease duration was 5.5 ± 4.4 years. More than 90% of the patients were at stage 1 or 2 of Hoehn and Yahr, and more than a quarter presented motor complications. 96.2% of patients from the cohort were taking dopaminergic medication. The scores on all the scales of the non-motor evaluation showed that non-motor burden was significantly higher in PD patients compared to controls and the percentage of patients with cognitive impairment (30.4% vs. 11.3%), depressive symptoms (50.2% vs. 20.9%), pain (57.2% vs. 31.6%), impulse control disorder (12.7% vs. 1.7%) and compulsive behaviour (7.2% vs. 1.7%) was significantly higher in the PD group (Table 3). Moreover, the number of pills taken per day, drugs including antidepressant agents (24.1% vs. 11.1%) and drugs including analgesics (24.4% vs. 14.5%) were higher in PD patients than in controls (Table 2).

Figure 2 shows the percentage of patients presenting each non-motor symptom from the Non-Motor Symptoms Scale (NMSS) versus controls. Whilst nocturia (43%) was the most frequent non-motor symptom reported in controls, fatigue (62.4%) and nocturia (60.9%) were the most prevalent in PD patients. Considering the different domains from the NMSS, the highest scores in patients were in domains 7 (urinary symptoms), 8 (sexual dysfunction) and 2 (sleep/fatigue) (Table 3). With regard to QoL, the most affected domains were 8 (bodily discomfort), 3 (emotional well-being) and 6 (cognition) in patients (Table 3). A strong correlation was observed between

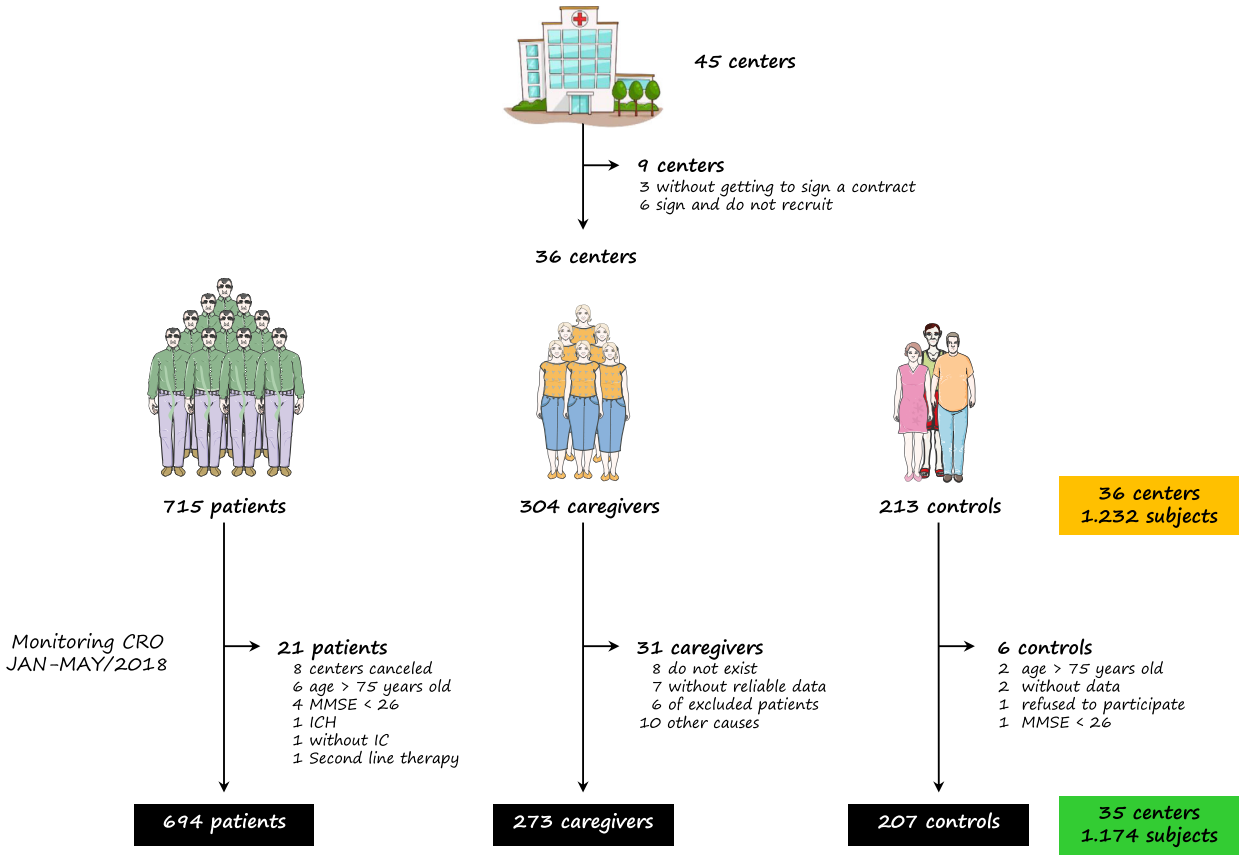

Figure 1 Flowchart on the monitoring process of the subjects participating in the COPPADIS-2015 study. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Sociodemographic variables in PD patients (n = 694) versus controls (n = 207); burden, mood, quality of life and sociodemographic characteristics in the principal caregiver's patient cohort (n = 273) is also represented

	Patients	Controls	Caregivers
Education level (%)			
Primary	42.1	31.4	41.9
Secondary	31.6	34.8	33.9
University	26.3	33.8	24.2
Civil status (%)			
Married	78	73.4	88
Single	7.1	9.2	7.1
Widowed	6.9	9.2	1.1
Divorced	6.8	6.8	2.6
Other	1.2	1.4	1.1
Living style (%)			
Alone	10.8	17.4	12.8
With a partner	79.1	73.4	20.4
With a son/daughter	5.2	5.3	66.8
Other	4.9	3.9	
Habitat (%)			
Rural (<5000)	11.6	9.2	12.8
Semi-urban (5000–20 000)	18.5	24.3	20.4
Urban (>20 000)	69.7	66.5	66.8
ZCBI (mean ± SD)	n. a.	n. a.	13.6 ± 12.2
No burden or very slight (0–20) (%)			76.9
Slight to moderate (21–40) (%)			19
Moderate to severe (41–60) (%)			3.6
Severe (61–88) (%)			0.3
CSI (mean ± SD)	n. a.	n. a.	2 ± 2.4
No high stress level (0–6) (%)			94.1
High stress level (7–13) (%)			5.9
BDI-II (mean ± SD)	8.7 ± 7.3	4.3 ± 5.5*	7.1 ± 7.7**
PQ-10 (mean ± SD)	7.3 ± 1.6	8.1 ± 1.2*	7.4 ± 1.6
EUROHIS-QOL8 (mean ± SD)	3.8 ± 0.6	4.2 ± 0.5*	3.9 ± 0.5

BDI-II, Beck Depression Inventory II; CSI, Caregiver Strain Index; PD, Parkinson's disease; PQ-10, a scale of global percieved QoL, from 0 (worst) to 10 (best); ZCBI, Zarit Caregiver Burden Inventory. The chi-squared, ANOVA and Mann–Whitney–Wilcoxon tests were applied. *P < 0.0001, differences between the three groups, controls versus patients and controls versus caregivers; **P = 0.002, difference between caregivers versus patients.

non-motor symptom burden (NMSS total score) and health-related QoL (39-item Parkinson's Disease Quality of Life Questionnaire Summary Index) (r = 72, P < 0.0001), non-motor symptom burden and mood (Beck Depression Inventory II) (r = 65, P < 0.0001) and mood and health-related QoL (r = 65, P < 0.0001).

Finally, with regard to the caregivers, 92.8% of them were living full-time with the patient, and the majority (76.9%) presented no burden or slight burden (Table 1).

Table 2 Comorbidities, PD and other health-related variables and therapies in patients (n = 694) and/or in controls (n = 207)

	Patients	Controls	P
Arterial hypertension (%)	33.6	31.9	0.733
Diabetes mellitus (%)	8.9	14	0.091
Dyslipidemia (%)	30.3	41.1	0.013
Cardiopathy (%)	8.1	5.8	0.475
Cardiac arrhythmia (%)	5	3.9	0.673
Smoking (%)			
No	60.5	52.7	0.109
Former smoker	30.1	33.3	
Smoker	9.2	14	
Alcohol consumption (%)			
No	79.1	77.8	0.761
Slight–moderate drinker	20.5	22.2	
Heavy drinker	0.3	0	
Years of disease from onset (mean ± SD)	5.5 ± 4.4	n. a.	
Hoehn and Yahr (mean ± SD)	2 ± 0.6	n. a.	
Stage 1 (%)	22.7	n. a.	
Stage 2 (%)	68	n. a.	
Stage 3 (%)	7.9	n. a.	
Stage 4–5 (%)	1.4	n. a.	
UPDRS-III (mean ± SD)	22.7 ± 11.2	n. a.	
UPDRS-IV (mean ± SD)	2 ± 2.4	n. a.	
Motor fluctuations (%)	33.9	n. a.	
Dyskinesia (%)	18.1	n. a.	
Treatment for PD (%)		n. a.	
Levodopa	72.9		
Dopamine agonists	69.2		
Pramipexole	34.9		
Ropinirole	17		
Rotigotine	16		
More than one at the same time	1.3		
MAO-B inhibitor	73.7		
COMT inhibitor	18.2		
Amantadine	7.8		
Anticholinergic drug	3		
Equivalent daily dose L-dopa (mg) (mean ± SD)	557 ± 412.1	n. a.	
Other treatments (%)			
Antidepressant	24.1	11.1	<0.0001
Benzodiazepine	15.7	12.1	0.372
Antipsychotic	2.2	0	0.088
Analgesic	24.4	14.5	0.008
Total number of drugs (mean ± SD)	5 ± 2.7	2.2 ± 2.4	<0.0001
Total number of pills (mean ± SD)	7.3 ± 4.1	2.5 ± 2.9	<0.0001
Number of anti-PD drugs (mean ± SD)	2.4 ± 1.1	n. a.	
Number of anti-PD pills (mean ± SD)	4.7 ± 2.8	n. a.	
Complementary therapies (%)			
Physiotherapy	28.4	7.4	<0.0001
Exercise	69.8	61.3	0.057

(continued)

Table 2 *(Continued)*

	Patients	Controls	*P*
Speech therapy	11.3	0.5	<0.0001
Cognitive stimulation	15.9	11.8	0.300
B vitamin supplements	5.5	1.5	0.047

COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase B; n. a., not applicable; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale. The chi-squared and Mann–Whitney–Wilcoxon tests were applied. Data about Hoehn and Yahr and UPDRS-III are during the OFF state (first thing in the morning without taking medication in the previous 12 h).

Discussion

The present study shows that different non-motor symptoms are frequently present in PD patients and are more prevalent than in controls. The COPPADIS-2015 includes more than 1000 subjects (694 patients, 273 caregivers and 207 controls) recruited from 35 centres of Spain in whom information about motor, non-motor symptoms, disability and QoL has been obtained with up to 20 scales, questionnaires and/or other tools used at baseline visits. As a whole, the clinical characteristics and assessment results of our PD sample were similar to those of previous comprehensive studies [8–14]. Our findings indicate as is well known that PD is not only a motor disorder and that PD patients suffer from different non-motor symptoms even during the first steps of the disease [15,16]. Although 90% of PD patients from our cohort were in early stages of the disease (Hoehn and Yahr stage 1 or 2), cognitive impairment, fatigue, pain, depressive symptoms, sleep problems or impulse behaviours affected at least one in three or four patients. Non-motor symptom frequency, according to the NMSS, showed excessive daytime sleepiness, fatigue, urinary symptoms, pain and loss of taste or smell as the most frequent non-motor symptoms reported; this aligns with previous studies [3,8,15–17]. Comparing burden severity between different domains of the NMSS, urinary and sexual symptoms, sleep/fatigue and miscellaneous presented the highest burden. Cardiovascular and perceptual problems/hallucinations were the domains with the lowest burden of symptoms, as has been reported before [4,17]. Previous studies have demonstrated that non-motor symptom burden is higher in PD patients than in controls [17]. However, even though early identification and proper management of non-motor symptoms should be a priority in daily clinical practice [18], frequently, non-motor symptoms are underdiagnosed [19]. In this sense, the characteristics of the assessment (e.g. the use of screening instruments, the presence of the caregiver etc.) can influence the diagnosis. It is well known that the Mini-Mental State Examination is not sensitive for detecting cognitive problems in PD. From our cohort, around 30% of patients presented with cognitive impairment when the Parkinson's Disease Cognitive Rating Scale was used (all with a Mini-Mental State Examination score ≥ 26), and especially relevant was the difference in fronto-subcortical function between patients and controls. It is known that executive dysfunction can be present from the early stages of Parkinson's disease. Other non-motor symptoms, such as impulse control disorder, pain or depression, were very frequent problems in our cohort, as in previous studies, when the screening tools were applied properly [20–22]. In particular, the prevalence of major, minor and sub-threshold depression was more than double in patients than in controls. Nevertheless, not only do non-motor symptoms go unrecognized in clinical practice. Other motor problems, such as motor fluctuations, dyskinesia, freezing or falls, are also not recognized. In our cohort, although it is a sample without a long disease duration – 5 years from symptoms onset – and almost 30% of the patients had not started with levodopa yet, at least one in three patients presented motor complications. Previous studies have observed that, in the early stages of PD, wearing off is already common and is underestimated by routine neurological clinical evaluation [23].

Another important aspect in PD patients is QoL because there is no cure for PD at present. Available therapies are aimed at improving symptoms experienced by the patients, their health status, degree of autonomy and QoL, but do not impede the progression of the disorder. In our sample, pain and discomfort, emotional well-being, cognition, activities of daily living and mobility were the most affected domains whereas social support, communication and stigma were least, aligning with previous reports [3]. It is known that depression and non-motor symptom burden are directly related to QoL and negatively impact both health-related and global QoL [3,24]. This is consistent with our observations that mood and non-motor symptom burden correlated strongly with QoL. With this association in mind, it has also been observed that patient QoL is correlated to the caregiver's status [25]. Interventions targeted at improving caregiver burden in order to also improve the patient's QoL have been suggested [26]. In our cohort, the percentage of caregivers with moderate to severe burden and high stress level was low, but their mood status and perception about their QoL was nearer to the patients than the controls. Finally, comorbidity and polypharmacy are important aspects to consider in PD patients because both influence the

Table 3 Non-motor, quality of life and disability assessment of PD patients (n = 694) and controls (n = 207)

	Patients	Controls	P
MMSE (mean ± SD)	29.2 ± 1	29.5 ± 0.8	<0.0001
PD-CRS (mean ± SD)	91.3 ± 15.8	99.3 ± 13.6	<0.0001
Fronto-subcortical (mean ± SD)	63.7 ± 14.4	70.8 ± 12.9	<0.0001
Posterior cortical (mean ± SD)	27.6 ± 3.6	28.5 ± 8.5	<0.0001
Cognitive status (%)			
Normal (PD-CRS > 84)[a]	69.6	88.7	<0.0001
MCI (PD-CRS 65–84)[a]	29.7	11.3	
Dementia (PD-CRS ≤ 64)[a]	0.7	0	
Puzzle (time of resolution) (mean ± SD)	5 ± 3.3	3.5 ± 1.8	<0.0001
NMSS (mean ± SD)	45.4 ± 38.1	14.5 ± 18.6	<0.0001
Cardiovascular (mean ± SD)	5.9 ± 10.2	2 ± 5.1	<0.0001
Sleep/fatigue (mean ± SD)	16.3 ± 16.1	5.6 ± 8.8	<0.0001
Mood/apathy (mean ± SD)	11.4 ± 16.4	3.6 ± 8.8	<0.0001
Perceptual symptoms (mean ± SD)	3.2 ± 8.9	0.2 ± 1.6	<0.0001
Attention/memory (mean ± SD)	10 ± 14.1	4.8 ± 9.7	<0.0001
Gastrointestinal symptoms (mean ± SD)	9.9 13.2	1.6 ± 5	<0.0001
Urinary symptoms (mean ± SD)	21.8 ± 22.5	6.7 ± 11.8	<0.0001
Sexual dysfunction (mean ± SD)	18.9 ± 25.6	9.3 ± 18.4	<0.0001
Miscellaneous (mean ± SD)	14.9 ± 15.5	3.5 ± 7.9	<0.0001
BDI-II (mean ± SD)	8.7 ± 7.3	4.3 ± 5.5	<0.0001
Depression[a] (%)	50.2	20.9	
Major[a]	16.1	7.8	
Minor[a]	16.7	7.3	
Subthreshold[a]	17.4	5.8	<0.0001
NPI – subject (mean ± SD)	6.1 ± 8.1	2.9 ± 6.1	<0.0001
QUIP-RS (mean ± SD)	4.3 ± 8.3	1.3 ± 3.5	<0.005
Subjects with ICD[b] (%)	12.7	1.7	<0.005
Subjects with CB[b] (%)	7.2	1.7	<0.0001
PDSS (mean ± SD)	114.9 ± 26.8	132.9 ± 16.4	<0.0001
Subjects with RBD (%)	39.2	2.9	<0.0001
VAS – Pain (mean ± SD)	2.7 ± 2.9	1.4 ± 2.4	<0.0001
Subjects with pain (%)	57.2	31.6	<0.0001
VAFS – physical (mean ± SD)	3 ± 2.8	1.2 ± 2.1	<0.0001
VAFS – mental (mean ± SD)	2.1 ± 2.5	1.1 ± 1.9	<0.0001
FOGQ (mean ± SD)	3.8 ± 4.6	0.15 ± 0.8	<0.0001
Subjects with falls (%)	13.2	1	<0.0001
ADLS ≥ 80% (%)	82.8	99.5	<0.0001
PDQ-39SI (mean ± SD)[c]	17.1 ± 13.5	4.4 ± 6.3	<0.0001
Mobility (mean ± SD)	16.6 ± 19.2	3 ± 9	<0.0001
Activities of daily living (mean ± SD)	18 ± 18.6	0.7 ± 2.6	<0.0001
Emotional well-being (mean ± SD)	21.5 ± 20	10.6 ± 16.2	<0.0001
Stigma (mean ± SD)	13.5 ± 19.5	0.4 ± 2.2	<0.0001
Social support (mean ± SD)	8.2 ± 16.5	3.2 ± 9.6	<0.0001
Cognition (mean ± SD)	19.3 ± 17.9	7.4 ± 12.1	<0.0001
Communication (mean ± SD)	10.2 ± 15.3	0.9 ± 2.8	<0.0001
Pain and discomfort (mean ± SD)	26.4 ± 22.8	9.4 ± 16.4	<0.0001
PQ-10 (mean ± SD)	7.3 ± 1.6	8.1 ± 1.2	<0.0001
EUROHIS-QOL8 (mean ± SD)	3.8 ± 0.6	4.2 ± 0.5	<0.0001
Quality of life (mean ± SD)	3.8 ± 0.7	4.2 ± 0.6	<0.0001
Health status (mean ± SD)	3.2 ± 0.9	4 ± 0.7	<0.0001
Energy (mean ± SD)	3.8 ± 0.8	4.2 ± 0.7	<0.0001
Autonomy for activities of daily living (mean ± SD)	3.6 ± 0.9	4.3 ± 0.7	<0.0001

(continued)

decisions made in daily clinical practice. It was observed that, as in previous studies [27], the number of drugs and pills taken per day was higher in PD patients than controls, including antidepressant agents and analgesics. As a whole, all these data reflect the concept of PD as a complex disorder with many

Table 3 *(Continued)*

	Patients	Controls	*P*
Self-esteem (mean ± SD)	3.8 ± 0.8	4.2 ± 0.7	<0.0001
Social relationships (mean ± SD)	4.1 ± 0.7	4.4 ± 0.6	<0.0001
Economic capacity (mean ± SD)	3.9 ± 0.8	4.2 ± 0.7	<0.0001
Habitat (mean ± SD)	4.2 ± 0.7	4.4 ± 0.6	<0.0001

ADLS, Schwab and England Activities of Daily Living Scale; BDI-II, Beck Depression Inventory II; CB, compulsive behaviour; FOGQ, Freezing of Gait Questionnaire; ICD, impulse control disorder; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index; PDSS, Parkinson's Disease Sleep Scale; PQ-10, a scale of global perceived QoL, from 0 (worst) to 10 (best); QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale; RBD, rapid eye movement behaviour disorder; VAFS, Visual Analog Fatigue Scale; VAS – Pain, Visual Analog Scale – Pain. The chi-squared and Mann–Whitney–Wilcoxon test were applied (except for fronto-subcortical and PD-CRS total scores in which Student's *t* test was applied because both variables presented a normal distribution). NMSS domains are expressed as a percentage (0–100). [a]According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) and Judd criteria; [b]pathological gambling, compulsive buying, binge eating and hypersexuality are included as ICDs whilst hobbism, punding, walkabout and dopaminergic dysregulation syndrome are considered CBs; dopaminergic dysregulation syndrome accounted for the investigator criterion; the validated test QUIP-RS for screening of ICDs and CBs (cutoff points: gambling ≥ 6, buying ≥ 8, sex ≥ 8, eating ≥ 7, hobbism-punding ≥ 7) was applied [34]; [c]for PDQ-39, $n = 168$ in the control group.

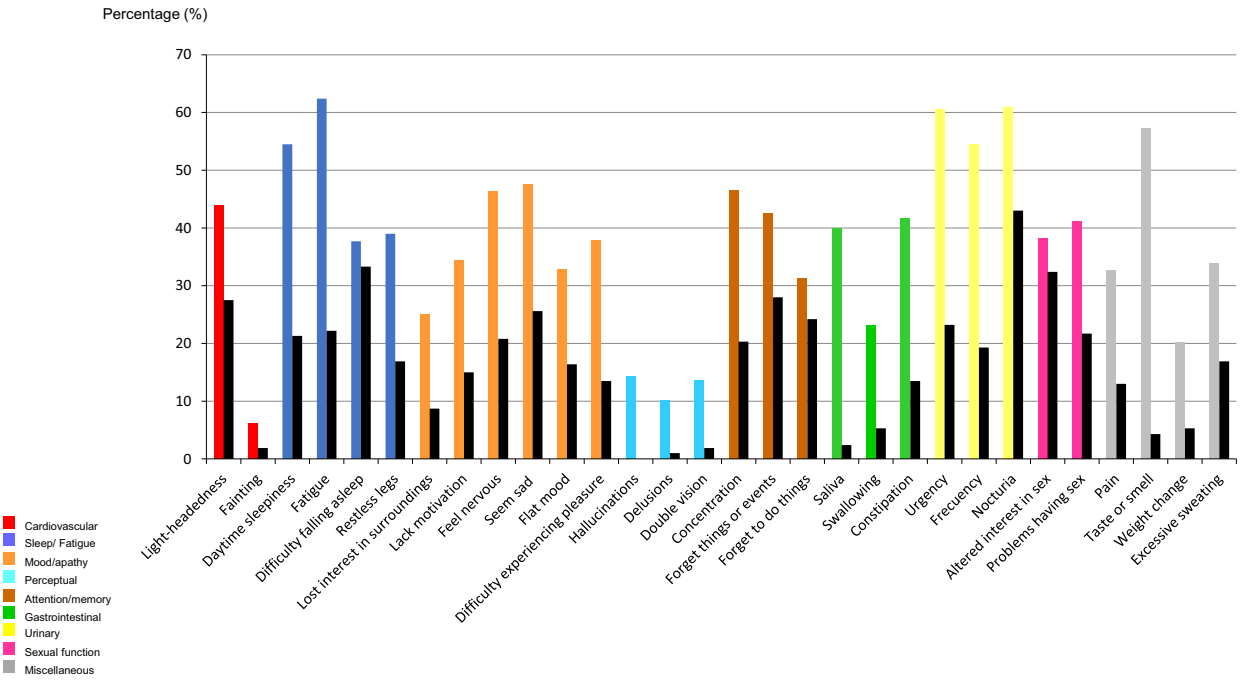

Figure 2 Frequency of different non-motor symptoms from the NMSS in patients (colour) and controls (black); the chi-squared test was applied; $P < 0.0001$ for all items except items 2 ($P = 0.018$), 5 ($P = 0.257$), 18 ($P = 0.052$) and 25 ($P = 0.124$). [Colour figure can be viewed at wileyonlinelibrary.com]

different symptoms and that exhaustive evaluation of the patient is the best way to try to comprehend what problems are causing disability and a poor QoL.

Nowadays, it is not clearly known what relationship exists between the progression of motor symptoms and non-motor symptoms in the long term. A current research priority in PD is to identify prognostic biomarkers [28]. To identify PD subtypes and factors influencing the disease course, multiple cohort studies have been designed globally [29,30]. In COPPADIS-2015, more than 300 participants completed blood analysis (serum biomarkers, genetic studies) and underwent cranial magnetic resonance imaging at baseline to be analysed to identify markers of prognostic value, either alone or in combination with clinical and/or paraclinical variables. Some examples are the genetic impact on cognition and brain function in newly diagnosed Parkinson's disease from the

ICICLE-PD study [31], the diffusion magnetic resonance imaging analysis technique as a neuroimaging marker of progression symptoms from the PPMI cohort [32], and different subtypes of mild cognitive impairment in patients with PD from the LANDSCAPE study [33]. A recent review [30] identified 44 cohort studies with a cumulative sample size of 14 666 participants. The cohorts' median participants were 138 (range from 23 to 3.090), the median follow-up interval was 1.5 years and the median planned observational period was 5 years (range from 1 to 20 years). Only 9% of the cohorts presented a sample size between 500 and 1000 participants and only 7% >1000. In comparison with other cohort studies, COPPADIS-2015 presents a large sample size, thorough annual evaluations, a control group and the inclusion of the principal caregiver of the patient, and the biomarkers included have some of the characteristics needed in an ideal marker (fast and affordable to obtain, available, repeatable and safe).

In conclusion, COPPADIS-2015 has been designed to provide additional knowledge about PD progression. Currently, extensive information is available about the baseline visits (cross-sectional study) that will be analysed in detail in the near future. The opportunities for collaborations based on existing PD cohort data are vast and growing to establish a comprehensive, up-to-date, open-access internet platform and database with interactive, easy-to-use search tools of PD cohort information and contact information [29]. Such (ongoing) collaborative efforts should be further encouraged. The first thing in any case is to have a large amount of data that can be used, properly collected from cohorts with a large number of participants. COPPADIS intends to be a contribution in this sense.

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Disclosure of conflicts of interest

Financial disclosure is given in Appendix S1.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Recruitment period was from January 2016 to October 2017 (baseline assessment of each participating subject). 1A, patient inclusion process and motor assessment by the principal investigator (neurologist who is an expert in movement disorders and Parkinson's disease); 2A, non-motor assessment by the principal investigator, specialized nurse, psychologist or fellow with adequate training; 2B, caregiver assessment; 2C, control assessment. *Only patients with motor fluctuations (UPDRS-IV) were assessed during the OFF medication (first thing in the morning without taking medication in the previous 12 h) and during the ON medication state.

Appendix S1. COPPADIS Study Group

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