

Research Report

Falls Predict Acute Hospitalization in Parkinson's Disease

Diego Santos García^{a,1,*}, Teresa de Deus Fonticoba^b, Carlos Cores^a, Ester Suárez Castro^b, Jorge Hernández Vara^c, Silvia Jesús^{d,e}, Pablo Mir^{d,e}, Marina Cosgaya^f, Maria José Martí^f, Pau Pastor^g, Iria Cabo^h, Manuel Seijo^h, Inés Legardaⁱ, Bárbara Vivesⁱ, Nuria Caballo^j, Javier Rúa Martínez^k, Ioana Croitoru^k, Esther Cubo^l, Javier Miranda^l, Maria Gema Alonso Losada^m, Carmen Labandeira^m, Nuria López Arizteguiⁿ, Mabel Morales-Casadoⁿ, Isabel González Aramburu^o, Jon Infante^o, Sonia Escalante^p, Noemí Bernardo^p, Marta Blázquez Estrada^q, Manuel Menéndez González^g, Juan García Caldentey^r, Carmen Borrué^s, Lydia Vela^t, Maria José Catalán^u, Víctor Gómez Mayordomo^u, Mónica Kurtis^v, Cristina Prieto^w, Carlos Ordás^w, Víctor Nogueira^x, Lydia López Manzanares^y, Maria Asunción Ávila Rivera^z, Victor Puente^{aa}, Jose Manuel García Moreno^{bb}, Berta Solano Vila^{cc}, María Álvarez Saucó^{dd}, Francisco Carrillo Padilla^{ee}, Juan Carlos Martínez Castrillo^{ff}, Pilar Sánchez Alonso^{gg}, Itziar Gastón^{hh}, Jaime Kulisevsky^{e,ii}, Caridad Valero^{jj}, Oriol de Fábregues^c, Jessica González Ardura^{kk}, Luis Manuel López Díaz^{ll}, Pablo Martinez-Martin^e and COPPADIS Study Group

^aCHUAC, Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain

^bCHUF, Complejo Hospitalario Universitario de Ferrol, A Coruña, Spain

^cNeurology Department and Neurodegenerative Diseases Research. Vall D'Hebron University Campus, Barcelona, Spain

^dUnidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain

^eCIBERNED (Centro de Investigación Biomédica en Red Enfermedades Neurodegenerativas), Spain

^fHospital Clínic de Barcelona, Barcelona, Spain

^gMovement disorders Unit, University Hospital Mutua de Terrassa, Barcelona, Spain

^hComplejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain

ⁱHospital Universitario Son Espases, Palma de Mallorca, Spain

^jConsorci Sanitari Integral, Hospital Moisès Broggi, Sant Joan Despí, Barcelona, Spain

^kHospital Universitario Donostia, San Sebastián, Spain

^lComplejo Asistencial Universitario de Burgos, Burgos, Spain

^mHospital Álvaro Cunqueiro, Complejo Hospitalario Universitario de Vigo (CHUVI), Vigo, Spain

ⁿComplejo Hospitalario de Toledo, Toledo, Spain

^oHospital Universitario Marqués de Valdecilla, Santander, Spain

^pHospital de Tortosa Verge de la Cinta (HTVC), Tortosa, Tarragona, Spain

^qHospital Universitario Central de Asturias, Oviedo, Spain

^rCentro Neurológico Oms, Palma de Mallorca, Spain

¹ORCID ID: 0000-0002-3126-5111.

*Correspondence to: Dr. Diego Santos García, Department of Neurology, Hospital Universitario de A Coruña (HUAC), Complejo Hospitalario Universitario de A Coruña (CHUAC), C/ As

Xubias 84, 15006, A Coruña, Spain. Tel.: +34 646173341; E-mail: diegosangar@yahoo.es.

^sHospital Infanta Sofía, Madrid, Spain

^tFundación Hospital de Alcorcón, Madrid, Spain

^uHospital Universitario Clínico San Carlos, Madrid, Spain

^vHospital Ruber Internacional, Madrid, Spain

^wHospital Rey Juan Carlos, Madrid, Spain

^xHospital Da Costa, Burela, Lugo, Spain

^yHospital Universitario La Princesa, Madrid, Spain

^zConsorti Sanitari Integral, Hospital General de L'Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain

^{aa}Hospital del Mar, Barcelona, Spain

^{bb}Hospital Universitario Virgen Macarena, Sevilla, Spain

^{cc}Institut d'Assistència Sanitària (IAS) - Institut Català de la Salut. Girona, Spain

^{dd}Hospital General Universitario de Elche, Elche, Spain

^{ee}Hospital Universitario de Canarias, San Cristóbal de la Laguna, Santa Cruz de Tenerife, Spain

^{ff}Hospital Universitario Ramón y Cajal, Madrid, Spain

^{gg}Hospital Universitario Puerta de Hierro, Madrid, Spain

^{hh}Complejo Hospitalario de Navarra, Pamplona, Spain

ⁱⁱHospital de Sant Pau, Barcelona, Spain

^{jj}Hospital Arnau de Vilanova, Valencia, Spain

^{kk}Hospital Universitario Lucus Augusti (HULA), Lugo, Spain

^{ll}Complejo Hospitalario Universitario de Orense (CHUO), Orense, Spain

Accepted 14 March 2021

Pre-press 7 April 2021

Published 31 January 2023

Abstract.

Background: There is a need for identifying risk factors for hospitalization in Parkinson's disease (PD) and also interventions to reduce acute hospital admission.

Objective: To analyze the frequency, causes, and predictors of acute hospitalization (AH) in PD patients from a Spanish cohort.

Methods: PD patients recruited from 35 centers of Spain from the COPPADIS-2015 (COhort of Patients with PARKinson's DIsease in Spain, 2015) cohort from January 2016 to November 2017, were included in the study. In order to identify predictors of AH, Kaplan-Meier estimates of factors considered as potential predictors were obtained and Cox regression performed on time to hospital encounter 1-year after the baseline visit.

Results: Thirty-five out of 605 (5.8%) PD patients (62.5 ± 8.9 years old; 59.8% males) presented an AH during the 1-year follow-up after the baseline visit. Traumatic falls represented the most frequent cause of admission, being 23.7% of all acute hospitalizations. To suffer from motor fluctuations (HR [hazard ratio] 2.461; 95% CI, 1.065–5.678; $p=0.035$), a very severe non-motor symptoms burden (HR [hazard ratio] 2.828; 95% CI, 1.319–6.063; $p=0.008$), falls (HR 3.966; 95% CI 1.757–8.470; $p=0.001$), and dysphagia (HR 2.356; 95% CI 1.124–4.941; $p=0.023$) was associated with AH after adjustment to age, gender, disease duration, levodopa equivalent daily dose, total number of non-antiparkinsonian drugs, and UPDRS-III-OFF. Of the previous variables, only falls (HR 2.998; 95% CI 1.080–8.322; $p=0.035$) was an independent predictor of AH.

Conclusion: Falls is an independent predictor of AH in PD patients.

Keywords: Falls, hospitalization, non-motor symptoms, Parkinson's disease, predictors

INTRODUCTION

Motor and non-motor symptoms (NMS) in Parkinson's disease (PD) progress as the disease advances, which leads to complications such as falls, fractures, or infections. As a consequence, PD patients are reported to have 1.44 times more hospital admissions when compared to age and sex-matched peers

[1, 2]. These admissions are associated with prolonged length-of-stay and increased morbidity and mortality [3–5]. Once PD patients are admitted to hospital, they have prolonged inpatient stays [6], poor motor outcomes, infections, prescription errors, and increased postoperative mortality [7–10]. Moreover, following a first hospital encounter, the rate of a second encounter increased to approximately 50% when

patients were followed into a second year [11]. Previous studies reported a significant economic burden from PD hospitalization as well [12, 13]. There is a need for identifying risk factors for hospitalization in PD and also interventions to reduce acute PD hospital admission [14].

The aim of the present study was (1) to analyze the frequency and causes of acute hospitalization in PD patients from a Spanish cohort followed for 1-year and (2) to identify predictors of acute hospitalization.

MATERIAL AND METHODS

PD patients recruited from 35 centers of Spain from the COPPADIS cohort [15], from January 2016 to November 2017, were included in the study. Methodology about COPPADIS-2015 study can be consulted in <https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-016-0548-9>. This is a multi-center, observational, longitudinal-prospective, 5-year follow-up study designed to analyze disease progression in a Spanish population of PD patients. All patients included were diagnosed according to UK PD Brain Bank criteria. Exclusion criteria were: atypical parkinsonism, dementia (Mini-Mental State Examination [MMSE] < 26), age < 18 or > 75 years, inability to read or understand the questionnaires, to be receiving any advanced therapy (continuous infusion of levodopa or apomorphine, and/or with deep brain stimulation at baseline), and the presence of comorbidity, sequelae, or any disorder that could interfere with the assessment.

The data for the present study was obtained from the baseline evaluation [15]. Patient baseline evaluation included staging of severity of disease (modified Hoehn & Yah [H&Y] scale), motor assessment (Unified Parkinson's Disease Rating Scale [UPDRS] part III and part IV, Freezing of Gait Questionnaire [FOG-Q]), non-motor symptoms (Non-Motor Symptoms Scale [NMSS], Parkinson's Disease Sleep Scale [PDSS], Visual Analog Scale-Pain [VAS-Pain], Visual Analog Fatigue Scale [VAFS]), cognition (MMSE, Parkinson's Disease Cognitive Rating Scale [PD-CRS], completing a simple 16-piece puzzle), mood and neuropsychiatric symptoms (Beck Depression Inventory-II [BDI-II], Neuropsychiatric Inventory [NPI], Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale [QUIP-RS]), disability (Schwab & England Activities of Daily Living Scale [S&E]), health related quality of life (QoL) (the

39-item Parkinson's disease Questionnaire [PDQ-39SI]), and global QoL (PQ-10, EUROHIS-QOL 8-item index [EUROHIS-QOL8]) [16]. Interviews were conducted to determine the presence of falls according to the definition for falls proposed by the Kellogg International Work Group on the prevention of falls by the elderly [17]: a fall is an unintentional or unexpected event, results in the person coming to rest on the ground or another lower level and is not the result of a major intrinsic event (such as a loss of consciousness) or an overwhelming external force. The event was considered when it was not something that happened for a specific reason some time ago but was a repeated abnormal phenomenon. A time frame was not defined but it was specifically asked about the presence and number of falls in the last month. Moreover, falls diary, calendar, or postcard were not used. In patients with motor fluctuations, the motor assessment was conducted during the OFF state (without medication in the last 12 hours) and during the ON state. However, in patients without motor fluctuations, the assessment was only performed without medication (first hour in the morning without taking medication in the previous 12 hours).

The patients were followed for 1-year after the baseline visit and information about hospital admission was collected. Specifically, the following hospitalization-related data were recorded: number of hospitalizations, hospital stay days, and reasons for hospital admission. Those patients with at least one acute hospitalization during the follow-up were defined as *Patients with acute hospitalization*, whereas those with non-acute hospitalization during the follow-up was defined as *Patients without acute hospitalization*. Therefore, those patients with one or more programmed admission but without any acute hospitalization were considered as *Patients without acute hospitalization*. Rehospitalization was not considered for the analysis. The reasons for hospital admissions were divided in three groups [18]: 1) Direct PD-related morbidity: motor complications, psychiatric symptoms, autonomic dysfunction, sensory symptoms, sleep disorders, and side effects of anti-parkinsonian drugs; 2) Indirect PD-related morbidity: traumas, pneumonia, and intestinal obstruction / gastroparesis; 3) Non-PD related causes.

Data analysis

Data were processed using SPSS 20.0 for Windows. For comparisons between patients with and

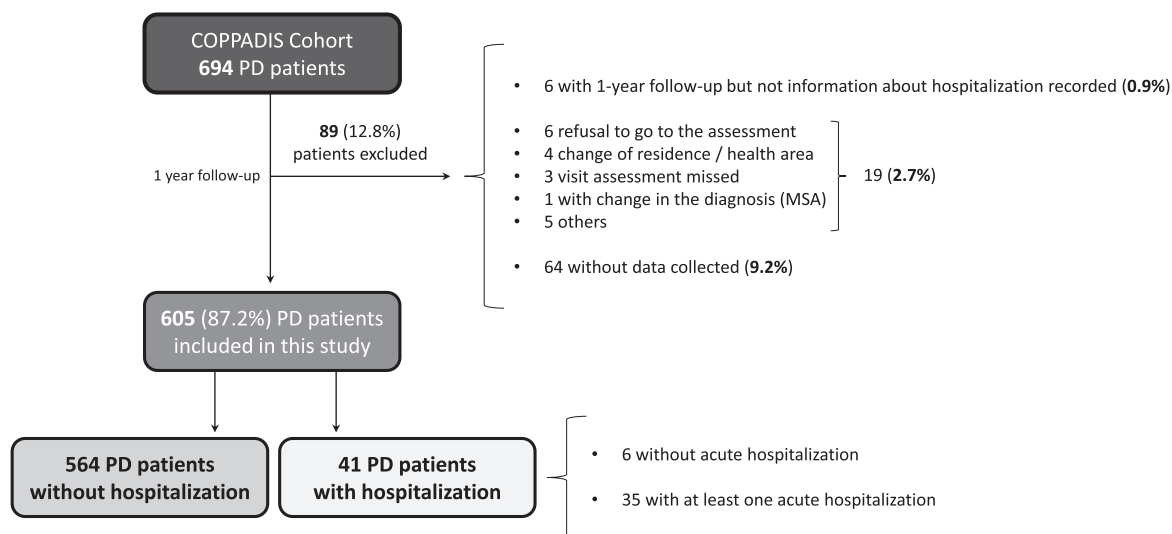


Fig. 1. Flowchart about PD patients from the COPPADIS cohort participating in the present study. Of 594 patients, 1 patient was excluded due to change in the diagnosis (from PD to MSA) and 88 for other reasons. Of 605 patients included in the analysis, 41 (6.8%) presented at least one hospitalization (35 acute and 6 planned hospitalization). MSA, multiple system atrophy; PD, Parkinson's disease.

without an acute hospitalization, the Student's *t*-test, Mann-Whitney-Wilcoxon test, Chi-square test, or Fisher test, as appropriate, were used (distribution for variables was verified by one-sample Kolmogorov-Smirnov test). Kaplan-Meier estimates were obtained to determine the risk of acute hospitalization with regards to the presence of different PD symptoms and/or complications: motor fluctuations; dyskinesia; very severe NMS (NMSS total score > 70) [19]; major depression [16]; cognitive impairment [20]; freezing of gait (FOG); falls; dysphagia. Self-reported FOG was defined regarding the FOG-Q as presenting with a FOG-Q item-3 score > 0. Functional dependency was defined as a S&E score less than 80% (80% = completely independent; 70% = not completely independent) [21]. Patients with a NMSS item-19 score > 0 were considered as suffering from dysphagia. Cox proportional hazards models were applied to identify independent predictors of acute hospitalization during the 1-year follow-up. Factors included as potential predictors were motor severity, motor complications, axial symptoms and related complications (FOG; falls; dysphagia), NMS burden, mood, cognition, neuropsychiatric symptoms, and disability for activities of daily living (Supplementary Table 1). Age, gender, disease duration, LEDD (levodopa equivalent daily dose [22]), and total number of non-antiparkinsonian drugs (as a marker of comorbidity [23]) were included as covariates (Supplementary Table 1). Values of $p < 0.05$ were considered significant.

Standard protocol approvals, registrations, and patient consents

For this study, we received approval from the *Comité de Ética de la Investigación Clínica de Galicia* from Spain (2014/534; 02/DEC/2014). 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.

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 605 (62.5 ± 8.9 years old; 59.8% males) from the 694 patients diagnosed with PD at baseline from the COPPADIS cohort were included in the analysis (87.2%). Figure 1 shows the reasons for the lack of follow-up of 89 patients. In 64 cases (9.2%) no data was recorded. The mean disease duration ($N = 605$) at baseline was 5.5 ± 4.4 years. Forty-one out of 605 PD patients (6.8%) presented at least one hospitalization during the 1-year follow-up after the baseline visit, being 35 of them (85.4%) with at least

one acute hospitalization. From the initial PD cohort (N=693; 1 case excluded due to change in diagnosis), 5% of the patients presented an acute hospitalization (Fig. 2A). In 35 out of 41 patients (85.4%) hospital admission was reported once, twice in 4 patients (9.8%), and three times in 2 patients (4.8%). The mean hospital stay days was 8.4 ± 8.3 (range 1–39). A total of 49 admissions were reported, being 38 acute and 11 programmed hospitalizations (Table 1). With regards to the acute admissions, 3 patients out of 35 (8.6%) were hospitalized due to a direct PD-related morbidity, 15 (42.9%) due to an indirect PD-related morbidity, and 14 (40%) due to non-PD related causes (Fig. 2B). Traumatic falls (9 events) represented the most frequent cause of admission, being 56.3% of all indirect PD-related morbidity causes, 23.7% all acute hospitalizations (38 events), and 18.4% of all hospitalizations (49 events) (Table 1 and Fig. 2C). No deaths were reported, neither in patients who presented a hospitalization nor in those who did not.

There were no differences between patients who presented an acute hospitalization compared to those who did not in terms of age, gender, disease duration, motor phenotype, and H&Y motor stage (Table 2). However, patients who suffered from an acute hospitalization presented a worse motor (UPDRS-III-OFF and UPDRS-IV) and non-motor status (PD-CRS, NMSS, BDI-II, NPI, and PDSS) at baseline (Table 2). Motor fluctuations, dyskinesia, falls, dysphagia,

Table 1
Causes of hospitalization during the 1 year follow-up after the baseline visit: 49 events in 41 PD patients

Acute unplanned hospitalizations (38 events)

Direct disease related morbidity (4 events)
-DBS PD system infection (2 events)
-Motor impairment(1 event)
-Orthostatic hypotension (1 event)
Indirect disease related morbidity (16 events)
-Traumatic falls (9 events)
-Pneumonia and/or respiratory infection (4 events)
-Intestinal obstruction and/orgastroparesia (3 events)
Non-PD related causes (16 events)
-Other infections (6 events)
-Cardiac ischemic attack (3 events)
-Urinary system complications (3 events)
-Cardiac insufficiency (1 event)
-Syncope secondary to aortic stenosis (1 event)
-Stroke (1 event)
-Esophagitis (1 event)
Unclear diagnosis (2 events)

Programmed hospitalizations (11 events)

-Lumbar canal stenosis surgery (2 events)
-Deep brain stimulation surgery (2 events)
-Carotid bypass surgery (1 event)
-Aortic valve replacement (1 event)
-knee replacement surgery (1 event)
-Transurethral resection of the prostate (1 event)
-Urinary incontinence surgery (1 event)
-Carcinoma pulmonary resection (1 event)
-Apomorphine test (1 event)

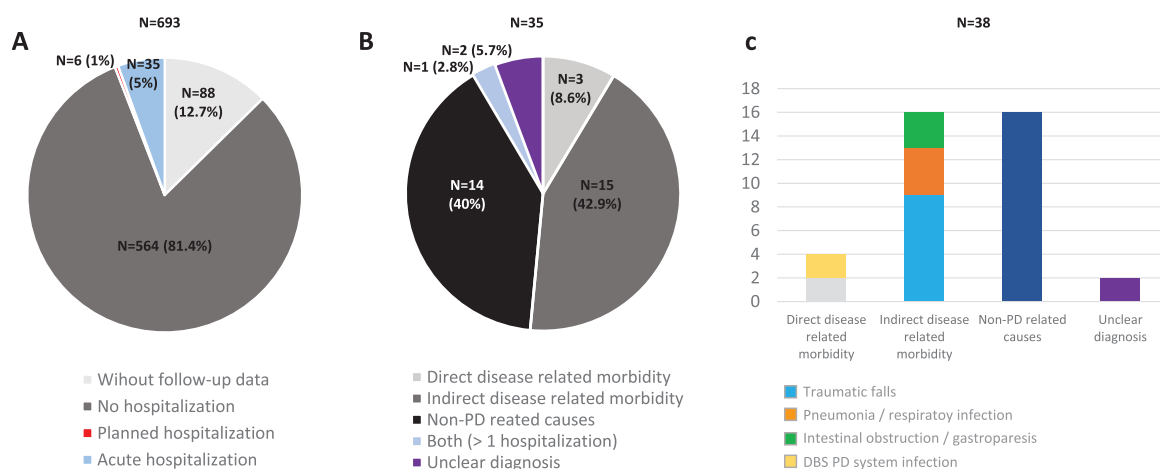


Fig. 2. A) Percentage of PD patients from the COPPADIS cohort (N=693; 1 excluded due to change in the diagnosis) without follow-up data (N=88; 12.7%), without hospitalization (N=564; 81.4%), with planned hospitalization (N=6; 1%), and with acute hospitalization (N=35; 5%) during the 1-year follow-up after the baseline visit. B) Percentage of patients with at least one acute hospitalization (N=35) regarding the reason of admission: Direct PD-related morbidity (N=3; 8.6%); Indirect PD-related morbidity (N=15; 42.9%); Non-PD related causes (N=14; 40%); More than 1 hospitalization with both reasons (N=1; 2.8%); Unclear diagnosis (N=2; 5.7%). C) Reasons for hospital admissions (38 events) in the subgroup of patients with acute hospitalization: 1) Direct PD-related morbidity (4 events; 10.5%); 2) Indirect PD-related morbidity: traumas, pneumonia, and intestinal obstruction / gastroparesis (16 events; 42.1%); 3. Non-PD related causes (16 events; 42.1%). PD, Parkinson's disease.

Table 2

Disease related characteristics, motor and non-motor symptoms, autonomy for activities of daily living and quality of life in PD patients with and without acute hospitalization during the year after the baseline visit ($n = 605$)

	All sample (N = 605)	Without acute hospitalization (N = 570)	With acute hospitalization (N = 35)	<i>p</i>
Age	62.5 ± 8.9	62.5 ± 8.9	63.5 ± 7.9	0.646
Males (%)	59.8	71.4	59.3	0.106
Disease duration (years)	5.5 ± 4.4	5.5 ± 4.3	5.8 ± 4.4	0.656
Number of non anti parkinsonian drugs	2.6 ± 2.4	2.6 ± 2.4	2.6 ± 2.5	0.980
L-dopa eq. daily dose (mg)	563.9 ± 420.5	555.8 ± 416.6	703.7 ± 468.4	0.063
Motor phenotype (%)				0.621
- Tremoricdominant	47.3	48.4	40	
- PIGD	38.8	37.8	45.7	
- Indeterminate	13.9	13.8	14.3	
Hoehn&Yahr	2 [2, 2]	2 [2, 2]	2 [2, 2]	0.720
- Stage from 3 to 5(%)	10.3	9.9	13.3	0.373
UPDRS-III	21.6 ± 10.4	20.7 ± 9.9	27.8 ± 11.8	0.001
UPDRS-IV	2 ± 2.4	1.8 ± 3.3	3.3 ± 3	0.001
- Motor fluctuations (%)	32.7	29.3	57.1	0.001
- Dyskinesia (%)	18.1	15.6	36.4	0.006
FOG-Q	3.5 ± 4.6	3.4 ± 4.5	4.7 ± 4.7	0.006
- Patients with FOG (%)	33.8	32.5	42.9	0.154
- Patients with falls (%)	17.5	15.5	31.4	0.020
PD-CRS	91.6 ± 15.3	92.2 ± 15.3	86.8 ± 13.9	0.049
- Cognitive impairment (PD-CRS ≤ 84) (%)	28	26.6	38.2	0.114
NMSS	44.8 ± 36.7	41.9 ± 35	66.1 ± 42.8	<0.0001
- Severe and/or NMS burden (NMSS > 40) (%)	40.7	37	67.6	0.001
- Very severe NMS burden (NMSS > 70) (%)	21.1	18.3	41.2	0.004
- Dysphagia	21.1	17.5	47.1	<0.0001
BDI-II	8.9 ± 7.7	8.4 ± 7.5	12.1 ± 8.5	0.007
- Major depression (%)	17.1	15.4	28.6	0.051
NPI	6.7 ± 8.4	6.2 ± 8.1	10.1 ± 9.4	0.005
QUIP-RS	4.3 ± 8.1	3.4 ± 7.1	4.5 ± 8	0.227
PDSS	118.1 ± 23.9	119.2 ± 23.7	110.9 ± 24.3	0.014
VAS-PAIN	2.8 ± 3	2.8 ± 3.1	3.4 ± 2.4	0.133
- Patients with pain (%)	61.2	58.9	77.1	0.027
VASF – physical	2.9 ± 2.8	2.9 ± 2.8	3.3 ± 2.8	0.342
VASF – mental	2.1 ± 2.6	2.1 ± 2.5	2.3 ± 2.9	0.668
ADLS	87.5 ± 10.9	87.9 ± 10.7	84.3 ± 11.4	0.048
- Patients with functional dependency (%)	12.1	11.4	17.1	0.233
PDQ-39SI	17.2 ± 14.1	15.9 ± 13.3	26.6 ± 16	<0.0001
PQ-10	7.2 ± 1.6	7.3 ± 1.6	6.8 ± 1.7	0.119
EUROHIS-QOL8	3.8 ± 0.5	3.8 ± 0.5	3.6 ± 0.6	0.038

The results represent percentages, mean ± SD or median [p25, p75]. Chi-squared and Mann-Whitney-Wilcoxon test were applied for comparisons between Non acute hospitalization (N = 570) and Acute unplanned hospitalization (N = 35) patients. Data about H&Y and UPDRS-III are during the OFF state (first thing in the morning without taking medication in the previous 12 hours). ADLS, Schwab and England Activities of daily living Scale); BDI, Beck Depression Inventory-II; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; 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; VASF, Visual Analog Fatigue Scale; VAS-Pain, Visual Analog Scale-Pain.

a severe and/or very severe NMS burden, and pain were more frequent in patients who presented an acute hospitalization compared to those who did not (Table 2). Specifically, the NMSS total score (66.1 ± 42.8 vs 41.9 ± 35 ; $p < 0.0001$) and the score on domains 2 (sleep/fatigue), 3 (mood/apathy), 4 (perceptual problems/hallucinations), 5 (attention/memory), 6 (gastrointestinal symptoms), and 7 (urinary symptoms) of the NMSS indicating

a greater severe burden were higher in patients with acute hospitalization (Fig. 3A and Supplementary Table 2). Moreover, QoL and disability were worse in this group of patients with acute hospitalization, presenting a higher score at baseline on the PDQ-39SI (26.6 ± 16 vs 15.9 ± 13.3 ; $p < 0.0001$) and a lower score on the EUROHIS-QOL8 (3.6 ± 0.6 vs 3.8 ± 0.5 ; $p = 0.038$) and S&E score (83.4 ± 11.4 vs 87.9 ± 10.7 ; $p = 0.048$) when compared with patients

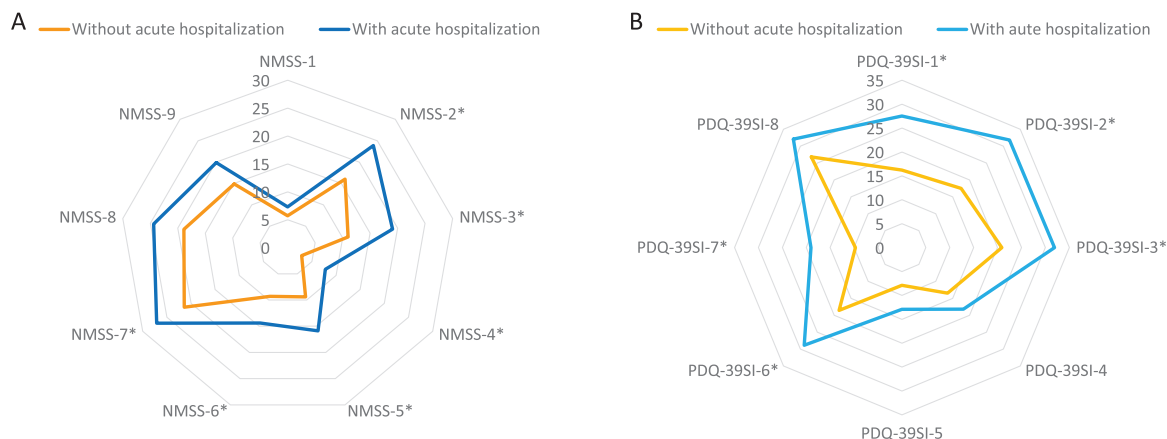


Fig. 3. A) Comparison in PD patients with vs without acute hospitalization of mean NMSS score on each domain of the scale at baseline; NMSS-1, Cardiovascular ($p=0.892$); 2) NMSS-2, Sleep/fatigue ($p=0.003$); NMSS-3, Depression/apathy ($p=0.003$); NMSS-4, Perceptual problems/hallucinations ($p=0.001$); NMSS-5, Attention/memory ($p=0.001$); NMSS-6, Gastrointestinal tract ($p=0.041$); NMSS-7, Urinary symptoms ($p=0.040$); NMSS-8, Sexual dysfunction ($p=0.152$); NMSS-9, Miscellaneous ($p=0.106$). B) Comparison in PD patients with vs without acute hospitalization of mean PDQ-39SI score on each domain of the scale: PDQ-39SI-1, Mobility ($p=0.001$); PDQ-39SI-2, Activities of daily living ($p=0.002$); PDQ-39SI-3, Emotional well-being ($p=0.002$); PDQ-39SI-4, Stigma ($p=0.153$); PDQ-39SI-5, Social support ($p=0.259$); PDQ-39SI-6, Cognition ($p=0.001$); PDQ-39SI-7, Communication ($p<0.0001$); PDQ-39SI-8, Pain and discomfort ($p=0.133$). NMS, Non-motor symptoms; PD, Parkinson's disease.

without acute hospitalization (Table 2). With regards to the domains of the PDQ-39SI, patients with acute hospitalizations presented significantly higher scores in all domains indicating a worse QoL except on domains 4 (stigma), 5 (social support), and 8 (pain/discomfort) (Fig. 3B and Supplementary Table 2).

In Kaplan-Meier analysis, the presence at baseline of motor fluctuations ($p=0.004$), dyskinesia ($p=0.003$), very severe NMS burden ($p=0.001$), major depression ($p=0.037$), falls ($p=0.001$), and dysphagia ($p=0.001$) was related to a higher risk of acute hospitalization (Fig. 4). Specifically, to suffer from motor fluctuations (HR [hazard ratio] 2.461; 95% CI, 1.065–5.678; $p=0.035$), a very severe NMS burden (HR [hazard ratio] 2.828; 95% CI, 1.319–6.063; $p=0.008$), falls (HR 3.966; 95% CI 1.757–8.470; $p=0.001$), and dysphagia (HR 2.356; 95% CI 1.124–4.941; $p=0.023$) was associated with acute hospitalization after adjustment to age, gender, disease duration, LEDD, total number of non-antiparkinsonian drugs, and UPDRS-III-OFF (Table 3). Patients who presented a score on the UPDRS-III-OFF >20 at baseline had a significantly higher risk of acute hospitalization after adjustment to the same covariates as well (HR 3.644; 95% CI 1.430–9.284; $p=0.007$). Although unadjusted HR associated with dyskinesia (HR 2.792; 95% CI 1.365–5.711; $p=0.005$) and major depression (HR 2.159; 95% CI 1.033–4.515; $p=0.041$) were significant (Table 3), the effect was not after adjustment to

the previous commented covariates. Of the previous variables, only falls (HR 2.998; 95% CI 1.080–8.322; $p=0.035$) was an independent predictor of acute hospitalization when different covariates as potential predictors of hospitalization were included in an “a priori” well-planned model (Table 4). In the model, having falls triples the probability of acute hospital admission regardless of other variables, and the frequency of falls at baseline was double in those patients who were admitted during the 1-year follow-up compared to those who did not (31.4% vs 15.5%; $p=0.020$). Specifically, having falls during the previous month to the baseline visit was associated with acute admission during the 1-year follow-up (Supplementary Figure 1).

DISCUSSION

In the present study, we observed different important findings: 1) the probability of presenting an acute hospitalization is not infrequent in patients with PD; 2) the QoL and autonomy for activities of daily living is worse and the NMS burden is greater in those PD patients who will have an acute hospitalization; 3) there are certain symptoms associated with a greater risk of acute hospitalization such as motor fluctuations, dyskinesias, severe NMS burden, major depression, falls, and dysphagia; 4) falls is an independent predictor of acute hospitalization that increases the risk by three times.

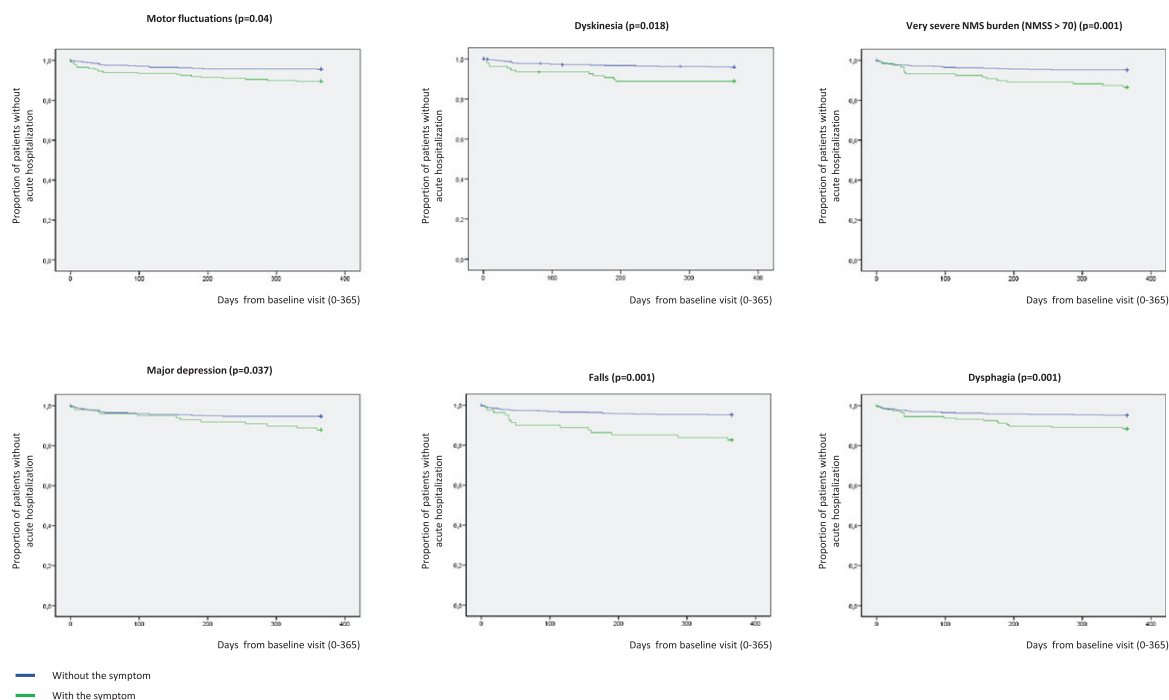


Fig. 4. Proportion of patients without acute hospitalization with regards to suffering (in blue) or not (in green) from motor fluctuations ($p=0.004$), dyskinesia ($p=0.003$), very severe NMS burden ($p=0.001$), major depression ($p=0.037$), falls ($p=0.001$), and dysphagia ($p=0.001$). Y, survival; X, days of follow-up. NMS, Non-motor symptoms.

Table 3

Analysis about the risk of acute hospitalization after 1 year of follow-up with regards to having or not different complications (N = 605)

	Unadjusted HR (95% CI)	p	Adjusted HR(95% CI)	p
Motor fluctuations	2.616 (1.329–5.148)	0.005	2.461 (1.065–5.678)	0.035
Dyskinesia	2.792 (1.365–5.711)	0.005	2.145 (0.905–5.085)	0.083
Severe or very severe NMSB (NMSS > 40)	2.871 (1.400–5.890)	0.004	2.645 (1.154–6.103)	0.022
Very severe NMSB (NMSS > 70)	2.925 (1.477–5.791)	0.002	2.828 (1.319–6.063)	0.008
FOG	1.489 (0.757–2.930)	0.249	1.117 (0.496–2.518)	0.789
Falls	3.262 (1.590–6.696)	0.001	3.966 (1.757–8.470)	0.001
Dysphagia	2.843 (1.450–5.575)	0.002	2.356 (1.124–4.941)	0.023
Major depression	2.159 (1.033–4.515)	0.041	1.934 (0.855–4.377)	0.113
Cognitive impairment (PD-CRS \leq 84)	1.493 (0.743–3.002)	0.260	1.160 (0.514–2.615)	0.721
HY-OFF from 3 to 5	1.331 (0.463–3.826)	0.595	0.703 (0.187–1.719)	0.602
UPDRS-III-OFF > 20	2.800 (1.258–6.233)	0.012	3.644 (1.430–9.284)	0.007*
Functional dependency	2.118 (0.877–5.116)	0.095	1.894 (0.675–5.318)	0.225

Age, gender, disease duration, LEDD (levodopa equivalent daily dose), total number of non-anti parkinsonian drugs (as a marker of comorbidity) and UPDRS-III-OFF were included in the model as covariates. *For this analysis the UPDRS-III-OFF was not included in the model. FOG, freezing of gait; HR, Hazard ratio; NMSB, non-motor symptoms burden; NMSS, Non-Motor Symptoms Scale; PD-CRS, Parkinson's Disease Cognitive Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

About 5% of the patients from the COPPADIS cohort [15, 16] presented an acute hospitalization after 1-year of follow-up. This percentage is low compared to other studies, ranging from 7 to 28% per year [17]. The results between studies vary in part to differences in methodology [1, 2, 24–27]. Moreover, many studies are prospective [6, 26, 28] or, more frequently, retrospective [29–34] analysis conducted

only in PD patients admitted with the aim to analyze problems during hospitalization. Moreover, several studies were conducted in small samples and/or without control group: 76 patients [28]; 108 patients [26]; 130 patients [25]; 132 patients [6]; 143 patients [33]; 144 patients [24]; 173 patients [30]; 367 patients [3]. A recent study conducted in a large population from North America, the Netherlands, and Israel showed

Table 4
Cox-regression model about predictors of acute hospitalization in PD patients after 1 year of follow-up (N = 605)

	HR (95% CI)	p
Age	1.002 (0.951–1.056)	0.937
Gender	0.627 (0.267–1.469)	0.282
Disease duration	0.838 (0.726–0.968)	0.016
LEDD	1.000 (0.999–1.001)	0.614
Total number of non-anti parkinsonian drugs	0.839 (0.675–1.042)	0.111
UPDRS-III-OFF	1.032 (0.991–1.074)	0.128
UPDRS-IV	1.071 (0.909–1.260)	0.413
NMSS	0.999 (0.989–1.009)	0.823
BDI-II	1.016 (0.955–1.081)	0.613
PD-CRS	0.986 (0.958–1.015)	0.339
NPI	1.021 (0.972–1.072)	0.406
Falls	2.998 (1.080–8.322)	0.035
Dysphagia	1.593 (0.645–3.932)	0.313
ADLS	1.004 (0.962–1.048)	0.865

Hazard ratio; LEED, Levodopa equivalent daily dose; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD-CRS, Parkinson's Disease Cognitive Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale. The omnibus test indicated an overall significant model $\chi^2 = 34,149$ ($p = 0.001$).

that of 4,680 PD patients followed during an average of 2 years (median 1.85, maximum 4.85 years), 2,264 patients (48.4%) had a hospital encounter after the baseline visit [35]. Compared with many other studies [6, 29, 30, 33, 34, 36, 37], the mean age of the patients from the COPPADIS cohort is lower, and, as previously reported [23, 38], our sample is not fully representative of the PD population due to inclusion and exclusion criteria at baseline (i.e., age limit, no dementia, no severe comorbidities, no second line therapies, etc.) which subsequently entails a bias toward early PD. This aspect may explain the lower frequency of admissions in our analysis after 1-year of follow-up. On the other hand, with regards to the causes of hospitalization, our findings are in line with two recent review studies [26, 39], in which infections, worsening motor features, falls/fractures, cardiovascular co-morbidities, neuropsychiatric, and gastrointestinal complications were the main reasons for hospitalization among people with PD. Specifically, in our study, falls was the most frequent cause despite more than 90% of the patients had a stage 2 of the H&Y. By the contrary, admissions related to a direct PD-related event were infrequent since ambulatory PD symptoms management is often preferred.

A worse QoL and a greater disability and NMS burden at baseline was observed in PD patients who presented an acute hospitalization in our study. We observe this finding because, unlike most other studies, the assessment at baseline was exhaustive

using different validated scales. Differences were observed between patients who were admitted during the follow-up and those who did not as those who were admitted had a worse motor and non-motor status and worse autonomy for activities of daily living and QoL. In other words, PD patients more affected by their disease may be more vulnerable and have a higher risk of acute hospitalization. Symptoms such as pain, dysphagia, falls, motor fluctuations, dyskinesia, a worse QoL, and a greater motor disability were more frequent in patients who presented an acute hospitalization, but no differences were observed in fatigue and motor phenotype. Falls, fractures, infections, cognitive, and motor decline have been identified as risk factors for acute hospital admissions in patients with PD [11, 14]. More specifically, longer timed up and go test, higher number of comorbidities, number of medications, the presence of motor fluctuations, having deep brain stimulation, and the degree of caregiver burden have been associated with hospitalization and/or rehospitalization in PD [35]. A higher PDQ-39 total score was observed to be associated with a higher risk of rehospitalization as well [35]. In our study, the factors associated with acute hospitalization are not surprising. However, the only independent predictor of hospitalization was falls. In this context, in a pooled data of 7 studies selected [27], the main causes of general ward admission were falls (30%) and PD-related causes (16%), whereas the main causes of neurological ward were motor (42.3%) and psychiatric complications (21.2%). In any case, our finding of falls as a predictor of acute hospitalization in PD should be interpreted with caution because the rates of admission due to fall (N = 9) were very low. Ideally, these findings should be reproduced over a longer period to capture more admission and arguably with patients with a broader range of severity.

A very important point is that some of these symptoms can be treated with the aim of reducing acute PD hospital admission [14]. For example, in our cohort, motor fluctuations were associated with a doubled probability of acute hospitalization, so reducing OFF time could reduce the risk. Many factors are correlated. Falls were associated with motor fluctuations (falls were present in 22.4% of patients with motor fluctuations compared to 8.5% of patients without them; $p < 0.0001$). One strategy for reducing them could be to increase the ON time in PD patients. However, falls can have different etiology. Optimizing motor symptom control and managing medication side effects may prevent falls and hence

hospital admissions [14]. Furthermore, physiotherapy is thought to improve PD motor symptoms, mobility, and balance [39], which also may reduce the risk of falls. However, there is a lack of evidence about interventions or negative results in the few trials performed [14]. In a randomized clinical trial comparing the incidence of pneumonia among 515 patients with dementia and PD who were randomized to either chin-down posture technique or two types of thickened fluids (nectar- and honey-thick consistencies) over a 3 month follow up period, at least one hospital admission was observed in 20% of each intervention arms [40]. Considering the complexity of managing PD, it is likely that a multimodal approach which addresses motor and non-motor complications, as well as palliatives aspects in end-stage disease, may be more effective compared to a single intervention approach [14, 41, 42]. The risk of acute hospitalization seems to be more related with PD symptoms, proper care, medication adherence, and comorbidity than age, gender or disease duration [4, 14, 26, 27, 41, 42]. Both patients who were admitted and those who were not had a similar mean disease duration. However, in the model and after adjustment to covariates related to disease progression, longer disease duration was associated with a lower risk of hospitalization. Lower risk of falls in more advanced patients because they have limited walking or prioritized care towards those with a more recent diagnosis could explain these findings.

The most important limitation of this study is the fact that information about admission in 88 of 693 PD patients was not recorded (12.7%). However, this is a limitation observed in other prospective studies. Of 7,507 PD patients, follow-up data was available only for 4,680 participants (62.3%) [35]. Although hospital admissions or mortality cannot be ruled out in this group from our study (N=88), there were no significant differences between this group and the rest of patients from the cohort with regards to age, disease duration, LEDD, and all the covariates included in the model (data not shown). A very important second limitation is that PD patients older than 75 years old were excluded from participation by COPPADIS study protocol [16], which is a major weakness because older patients with PD are more likely to have complex disease (cognitive impairment, high comorbidity, etc.) and falls. Other limitations are the bias toward early PD in this cohort, as we previously commented, and the lack of a control group. Moreover, falls diary, calendar, or postcard were not used [43] and a patient was considered to

suffer from falls based on the interview conducted. On the contrary, the strengths of our study include the large sample size, the prospective longitudinal follow-up design, the fact that this analysis was “a priori” planned as one objective of the multicenter COPPADIS project [16], and the extensive clinical and demographic information recorded.

In conclusion, this study observes that acute hospital admission is not infrequent in PD patients, that the risk is higher in patients with different complication (such as dysphagia, motor fluctuations, dyskinesia, and greater motor disability and NMS burden), and that falls is an independent predictor of acute hospitalization in PD patients. Future prospective studies are required to identify other predictors of acute hospitalization in PD and, more interestingly, to evaluate the effectiveness of proposed interventions over them.

ACKNOWLEDGMENTS

We would like to thank all patients and their caregivers who collaborated in this study. Many thanks also to *Fundación Española de Ayuda a la Investigación en Parkinson y otras Enfermedades Neurodegenerativas (Curemos el Parkinson; www.curemoselparkinson.org)*, Alpha Bioresearch (www.alpha-bioresearch.com), and other institutions helping us.

CONFLICT OF INTEREST

Santos García D. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, Italfarmaco, and Teva.

de Deus Fonticoba T: None.

Cores C. has received honoraria for educational presentations and advice service by Lundbeck and UCB Pharma.

Suárez Castro E: None.

Hernández Vara J. has received honoraria for advice service from Britannia, travel bursaries and educational grants from Abbvie, and has received honoraria for educational presentations from Abbvie, Teva, Bial, Zambon, Italfarmaco, and Sanofi-Genzyme.

Jesús S. has received honoraria from AbbVie, Bial, Merz, UCB, and Zambon and holds the competitive contract “Juan Rodés” supported by the Instituto de Salud Carlos III. She has received grants from the Spanish Ministry of Economy and Competitiveness (PI18/01898) and the Consejería de Salud de la Junta de Andalucía (PI-0459-2018).

Mir P. has received honoraria from AbbVie, Abbott, Allergan, Bial, Merz, UCB, and Zambon. He has received grants from the Spanish Ministry of Economy and Competitiveness [PI16/01575] co-founded by ISCIII (Subdirección General de Evaluación y Fomento de la Investigación) and by Fondo Europeo de Desarrollo Regional (FEDER), 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-0437-2012, PI-0471-2013], the Sociedad Andaluza de Neurología, the Jacques and Gloria Gossweiler Foundation, the Fundación Alicia Koplowitz, and the Fundación Mutua Madrileña.

Cosgaya M: None.

Martí MJ. received honoraria for advice and lecture from Abbvie, Bial, and Merzt Pharma and grants from Michael J. Fox Foundation for Parkinson Disease (MJFF): MJF_PPML10_001, PI044024; Fondo de Investigaciones Sanitarias of Spain (FIS PI17/00096) and from Generalitat de Catalunya (AGAUR Exp 2017 SGR 1502).

Pastor P: None.

Cabo I. has received honoraria for educational presentations and advice service by Abbvie, Zambon, and Bial.

Seijo M. has received honoraria for educational services from KRKA, UCB, Zambon, and Bial; travel grants from Daiichi and Roche.

Legarda I. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, and Teva.

Vives B: None.

Caballol N. has received honoraria from Bial, Italfarmaco, Qualigen, Zambon, UCB, Teva, and KRKA and sponsorship from Zambon, TEVA, and Abbvie for attending medical conferences.

Ruiz Martínez J. has received honoraria for educational presentations, attending medical conferences, and advice service by Abbvie, UCB Pharma, Zambon, Italfarmaco, Bial, and Teva.

Croitoru I: None.

Cubo E: Travel grants: Abbvie, Allergan, Boston; Lecturing honoraria: Abbvie, International Parkinson's disease Movement Disorder Society.

Miranda J: None.

Alonso Losada MG. has received honoraria for educational presentations and advice service by Zambon and Bial.

Labandeira C. has received honoraria for educational presentations and advice service by Abbvie, Italfarmaco, Zambon, and Bial.

López Ariztegui N. has received honoraria for educational presentations and advice service by Abbvie, Italfarmaco, Zambon, and Bial.

Morales-Casado M. has received honoraria for educational presentations and advice service by Bial, Zambon, UCB, Ferrer and Fresenius-kabi.

González Aramburu I: None.

Infante J. has received travel bursaries and honoraria for educational presentations from Abbvie and Zambon.

Escalante S. has received honoraria for educational presentations and advice service by Abbvie, Zambon, and Bial.

Bernardo N: None.

Blázquez Estrada M. has received honoraria for educational presentations and advice service by Abbvie, Abbott, UCB Pharma, Allergan, Zambon, Bial, and Qualigen.

Menéndez M. has received honoraria for educational presentations by KRKA and Zambon.

Seijo M. has received honoraria for educational services from KRKA, UCB, Zambon, and Bial; travel grants from Daiichi and Roche.

García Caldentey J. has received honoraria for educational presentations and advice service by Qualigen, Nutricia, Abbvie, Italfarmaco, UCB Pharma, Lundbeck, Zambon, Bial, and Teva.

Borrué C: None.

Vela L. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, and Teva.

Catalán MJ: None.

Gómez-Mayordomo V: None.

Kurtis M. has received honoraria from Bial, the Spanish Neurology Society and the International and Movement Disorders Society.

Prieto C: None.

Ordás C: None.

Nogueira V: None.

López Manzanares L: Compensated advisory services, consulting, research grant support, or speaker honoraria: AbbVie, Acorda, Bial, Intec Pharma, Italfarmaco, Pfizer, Roche, Teva, UCB, and Zambon.

Ávila Rivera MA. has received honoraria from Zambon, UCB Pharma, Qualigen, Bial, and Teva, and sponsorship from Zambon and Teva for attending conferences.

Puente V. has served as consultant for Abbvie and Zambon; has received grant/research from Abbvie.

García Moreno JM. has received honoraria for educational presentations and advice service by

Abbvie, Ital-Pharma, Lundbeck, Merz, KRKA, UCB, Pharma, Zambon, Bial and Teva.

Solano Vila B. has received honoraria for educational presentations and advice service by UCB, Zambon, Teva, Abbvie, and Bial.

Álvarez Sauco M. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, and Teva.

Carrillo Padilla F. has received honoraria from Zambon (SEN Congress assistance).

Martínez Castrillo JC. has received research support from Lundbeck, Italfarmaco, Allergan, Zambon, Merz, and Abbvie. He has also received speaking honoraria from AbbVie, Bial, Italfarmaco, Lundbeck, Krka, TEVA, UCB, Zambon, Allergan, Ipsen, and Merz.

Sánchez Alonso P. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, and Teva.

Gastón I. has received research support from Abbvie and Zambon and has served as a consultant for Abbvie, Exelts, and Zambon.

Kulisevsky J: (1) Consulting fees: Roche, Zambon; (2) Stock / allotment: No; (3) Patent royalties / licensing fees: No; (4) Honoraria (e.g., lecture fees): Zambon, Teva, Bial, UCB; (5) Fees for promotional materials: No; (6) Research funding: Roche, Zambon, Cibernet; Instituto de Salud Carlos III; Fundació La Marató de TV3; (7) Scholarship from corporation: No; (8) Corporate laboratory funding: No; (9) Others (e.g., trips, travel, or gifts): No.

Valero C. has received honoraria for educational services from Zambon, Abbvie and UCB.

de Fábregues O. has received honoraria for educational presentations and advice service by Bial, Zambon, Abbvie, KRKA, and Teva.

González Ardura J. has received honoraria for speaking from italoфарма, Krka, Genzyme, UCB, Esteve, Psyma iberica marketing research SL and Ferrer, course grant from Teva and travel grant from Merck.

López Díaz L. has received honoraria from UCB, Lundbeck and KRKA.

Martínez-Martin P. has received honoraria from Editorial Viguera and Takeda Pharmaceuticals for lecturing in courses; from Britannia for writing an article in their Parkinson's Disease Medical Journal-Kinetic; and from the International Parkinson and Movement Disorder Society (MDS) for management of the Program on Rating Scales. Grants from the

MDS for development and validation of the MDS-NMS.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JPD-212539>.

REFERENCES

- [1] Guttman M, Slaughter PM, Theriault ME, DeBoer DP, Naylor CD (2003) Burden of parkinsonism: A population-based study. *Mov Disord* **18**, 313-319.
- [2] Aminoff MJ, Christine CW, Friedman JH, Chou KL, Lyons KE, Pahwa R, Bloem BR, Parashos SA, Price CC, Malaty IA, Ianse R, Bodis-Wollner I, Suchowersky O, Oertel WH, Zamudio J, Oberdorf J, Schmidt P, Okun MS; National Parkinson Foundation Working Group on Hospitalization in Parkinson's Disease (2011) National Parkinson Foundation Working Group on Hospitalization in Parkinson's Disease. Management of the hospitalized patient with Parkinson's disease: Current state of the field and need for guidelines. *Parkinsonism Relat Disord* **17**, 139-145.
- [3] Woodford H, Walker R (2005) Emergency hospital admissions in idiopathic Parkinson's disease. *Mov Disord* **20**, 1104-1108.
- [4] Low V, Ben-Shlomo Y, Coward E, Fletcher S, Walker R, Clarke CE (2015) Measuring the burden and mortality of hospitalisation in Parkinson's disease: A cross-sectional analysis of the English Hospital Episodes Statistics database 2009-2013. *Parkinsonism Relat Disord* **21**, 449-454.
- [5] Ahlskog JE (2014) Parkinson disease treatment in hospitals and nursing facilities: Avoiding pitfalls. *Mayo Clin Proc* **89**, 997-1003.
- [6] Martignoni E, Godi L, Citterio A, Zangaglia R, Riboldazzi G, Calandrella D, Pacchetti C, Nappi G; Parkinson's Disease Comorbidity Study Group (2004) Comorbid disorders and hospitalisation in Parkinson's disease: A prospective study. *Neurol Sci* **25**, 66-71.
- [7] Dorton DM (1995) The care of patients with Parkinson's disease. *J Post Anesth Nurs* **10**, 102-106.
- [8] Vergenz S (2007) Caring for the Parkinson's patient: A nurse's perspective. *Dis Mon* **53**, 243-251.
- [9] Stotz M, Thummler D, Schurch M, Renggli JC, Urwyler A, Pargger H (2004) Fulminant neuroleptic malignant syndrome after perioperative withdrawal of antiParkinsonian medication. *Br J Anaesth* **93**, 868-871.
- [10] Antonini A, Miro L, Castiglioni C, Pezzoli G (2008) The rationale for improved integration between home care and neurology hospital services in patients with advanced Parkinson's disease. *Neurol Sci* **29**(Suppl 5), S392-S396.
- [11] Hassan A, Wu SS, Schmidt P, Dai Y, Simuni T, Giladi N, Bloem BR, Malaty IA, Okun MS; NPF-QII Investigators (2013) High rates and the risk factors for emergency room visits and hospitalization in Parkinson's disease. *Parkinsonism Relat Disord* **19**, 949-954.
- [12] Huse DM, Schulman K, Orsini L, Castelli-Haley J, Kennedy S, Lenhart G (2005) Burden of illness in Parkinson's disease. *Mov Disord* **20**, 1449-1454.
- [13] Davis KL, Edin HM, Allen JK (2010) Prevalence and cost of medication nonadherence in Parkinson's disease:

- Evidence from administrative claims data. *Mov Disord* **25**, 474-480.
- [14] Muzerengi S, Herd C, Rick C, Clarke CE (2016) A systematic review of interventions to reduce hospitalisation in Parkinson's disease. *Parkinsonism Relat Disord* **24**, 3-7.
- [15] Santos García D, Jesús S, Aguilar M, Planellas LL, García Caldentey J, Caballol N, Legarda I, Hernández Vara J, Cabo I, López Manzanares L, González Aramburu I, Ávila Rivera MA, Catalán MJ, López Díaz L, Puente V, García Moreno JM, Borrué C, Solano Vila B, Álvarez Saucó M, Vela L, Escalante S, Cubo E, Carrillo Padilla F, Martínez Castrillo JC, Sánchez Alonso P, Alonso Losada MG, López Ariztegui N, Gastón I, Kulisevsky J, Menéndez González M, Seijo M, Rúa Martínez J, Valero C, Kurtis M, de Fábregues-Boixar O, González Ardura J, Prieto Jurczynska C, Martínez-Martin P, Mir P; COPPADIS Study Group (2019) 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. *Eur J Neurol* **26**, 1399-1407.
- [16] Santos-García D, Mir P, Cubo E, Vela L, Rodríguez-Oroz MC, Martí MJ, Arbelo JM, Infante J, Kulisevsky J, Martínez-Martin P; COPPADIS Study Group (2016) COPPADIS-2015 (COhort of Patients with Parkinson's Disease in Spain, 2015), a global-clinical evaluations, serum biomarkers, genetic studies and neuroimaging-prospective, multicenter, non-interventional, long-term study on Parkinson's disease progression. *BMC Neurol* **16**, 26.
- [17] Gibson M, Andres R, Isaacs B, Radebaugh T, Worm-Peterson J (1987) The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Danish Med Bull* **34**(Suppl 4), 1-24.
- [18] Gerlach OH, Winogrodzka A, Weber WE (2011) Clinical problems in the hospitalized Parkinson's disease patient: Systematic review. *Mov Disord* **26**, 197-208.
- [19] Martínez-Martin P, Ray Chaudhuri K (2018) Comprehensive grading of Parkinson's disease using motor and non-motor assessments: Addressing a key unmet need. *Expert Rev Neurother* **18**, 41-50.
- [20] Pagonabarraga J, Kulisevsky J, Llebaria G, García-Sánchez C, Pascual-Sedano B, Gironell A (2008) Parkinson's disease-cognitive rating scale: A new cognitive scale specific for Parkinson's disease. *Mov Disord* **23**, 998-1005.
- [21] Santos-García D, de Deus-Fonticoba T, Suárez Castro E, M Aneiros Díaz Á, Feal-Painceiras MJ, Paz-González JM, García-Sancho C, Jesús S, Mir P, Planellas L, García-Caldentey J, Caballol N, Legarda I, Hernández-Vara J, González-Aramburu I, Ávila-Rivera MA, Catalán MJ, Nogueira V, Álvarez-Saucó M, Vela L, Escalante S, Cubo E, Sánchez-Alonso P, Alonso-Losada MG, López-Ariztegui N, Martínez-Martin P; COPPADIS Study Group (2020) The impact of freezing of gait on functional dependency in Parkinson's disease with regard to motor phenotype. *Neurol Sci* **41**, 2883-2292.
- [22] Schade S, Mollenhauer B, Trenkwalder C (2020) Levodopa equivalent dose conversion factors: An updated proposal including opicapone and safinamide. *Mov Disord Clin Pract* **7**, 343-345.
- [23] Santos García D, de Deus Fonticoba T, Suárez Castro E, Borrué C, Mata M, Solano Vila B, Cots Foraster A, Álvarez Saucó M, Rodríguez Pérez AB, Vela L, Macías Y, Escalante S, Esteve P, Reverté Villarroya S, Cubo E, Casas E, Arnaiz S, Carrillo Padilla F, Pueyo Morlans M, Mir P, Martínez-Martin P; COPPADIS Study Group (2019) Non-motor symptoms burden, mood, and gait problems are the most significant factors contributing to a poor quality of life in non-demented Parkinson's disease patients: Results from the COPPADIS Study Cohort. *Parkinsonism Relat Disord* **66**, 151-157.
- [24] Vargas AP, Carod-Artal FJ, Nunes SV, Melo M (2008) Disability and use of healthcare resources in Brazilian patients with Parkinson's disease. *Disabil Rehabil* **30**, 1055-1062.
- [25] Cosentino M, Martignoni E, Michielotto D, Calandrella D, Riboldazzi G, Pacchetti C, Frigo G, Nappi G, Lecchini S (2005) Medical healthcare use in Parkinson's disease: Survey in a cohort of ambulatory patients in Italy. *BMC Health Serv Res* **5**, 26.
- [26] Vossius C, Nilsen OB, Larsen JP (2010) Parkinson's disease and hospital admissions: Frequencies, diagnoses and costs. *Acta Neurol Scand* **121**, 38-43.
- [27] Koay L, Rose J, Abdelhafiz AH (2018) Factors that lead to hospitalisation in patients with Parkinson disease-A systematic review. *Int J Clin Pract* **72**, doi: 10.1111/ijcp.13039
- [28] Guneyel O, Onultan O, Onur O (2008) Parkinson's disease and the frequent reasons for emergency admission. *Neuropsychiatr Dis Treat* **4**, 711-714.
- [29] Kessler II (1972) Epidemiologic studies of Parkinson's disease. II. A hospital-based survey. *Am J Epidemiol* **95**, 308-318.
- [30] Tan LC, Tan AK, Tjia HT (1998) The profile of hospitalised patients with Parkinson's disease. *Ann Acad Med Singapore* **27**, 808-812.
- [31] Temlett JA, Thompson PD (2006) Reasons for admission to hospital for Parkinson's disease. *Intern Med J* **36**, 524-526.
- [32] Louis ED, Henchcliffe C, Bateman BT, Schumacher C (2007) Young onset Parkinson's disease: Hospital utilization and medical comorbidity in a nationwide survey. *Neuroepidemiology* **29**, 39-43.
- [33] Klein C, Prokhorov T, Miniovitz A, Dobronevsky E, Rabey JM (2009) Admission of Parkinsonian patients to a neurological ward in a community hospital. *J Neural Transm* **116**, 1509-1512.
- [34] Lubomski M, Rushworth RL, Tisch S (2015) Hospitalisation and comorbidities in Parkinson's disease: A large Australian retrospective study. *J Neurol Neurosurg Psychiatry* **86**, 324-330.
- [35] Shahgholi L, De Jesus S, Wu SS, Pei Q, Hassan A, Armstrong MJ, Martínez-Ramírez D, Schmidt P, Okun MS (2017) Hospitalization and rehospitalization in Parkinson disease patients: Data from the National Parkinson Foundation Centers of Excellence. *PLoS One* **12**, e0180425.
- [36] Paul BS, Paul G, Singh G, Kaushal S, Verma U (2017) Pattern of hospital admission and outcome in Parkinson's disease: A study from Punjab, India. *Neurol Asia* **22**, 33-39.
- [37] Braga M, Pederzoli M, Antonini A, Beretta F, Crespi V (2014) Reasons for hospitalization in Parkinson's disease: A case-control study. *Parkinsonism Relat Disord* **20**, 488-492; discussion 488.
- [38] Santos-García D, Castro ES, de Deus Fonticoba T, Painceiras MJF, Enriquez JGM, González JMP, Bartolomé CC, Planellas LL, Caldentey JG, Caballol N, Legarda I, López IC, Manzanares LL, Rivera MAÁ, Catalán MJ, Nogueira V, Borrué C, Saucó MA, Vela L, Cubo E, Castrillo JCM, Alonso PS, Losada MGA, Ariztegui NL, Gastón MI, Kulisevsky J, Pagonabarraga J, Seijo M, Martínez JR, Valero C, Kurtis M, Ardura JG, Prieto C, Mir P, Martínez-Martin P (2020) Sleep problems are related to a worse

- quality of life and a greater non-motor symptoms burden in Parkinson's disease. *J Geriatr Psychiatry Neurol*, doi: 10.1177/0891988720964250
- [39] Tomlinson CL, Patel S, Meek C, Clarke CE, Stowe R, Shah L, Sackley CM, Deane KH, Herd CP, Wheatley K, Ives N (2012) Physiotherapy versus placebo or no intervention in Parkinson's disease. *Cochrane Database Syst Rev* **7**, CD002817.
- [40] Robbins J, Gensler G, Hind J, Logemann JA, Lindblad AS, Brandt D, Baum H, Liliensfeld D, Kosek S, Lundy D, Dikeman K, Kazandjian M, Gramigna GD, McGarvey-Toler S, Miller Gardner PJ (2008) Comparison of 2 interventions for liquid aspiration on pneumonia incidence: A randomized trial. *Ann Intern Med* **148**, 509-518.
- [41] Kulkarni AS, Balkrishnan R, Anderson RT, Edin HM, Kirsch J, Stacy MA (2008) Medication adherence and associated outcomes in medicare health maintenance organization-enrolled older adults with Parkinson's disease. *Mov Disord* **23**, 359-365.
- [42] Bloem BR, Henderson EJ, Dorsey ER, Okun MS, Okubadejo N, Chan P, Andrejack J, Darweesh SKL, Munneke M (2020) Integrated and patient-centred management of Parkinson's disease: A network model for reshaping chronic neurological care. *Lancet Neurol* **19**, 623-634.
- [43] Allen NE, Schwarzel AK, Canning CG (2013) Recurrent falls in Parkinson's disease: A systematic review. *Parkinsons Dis* **2013**, 906274.

APPENDIX 1. COPPADIS STUDY GROUP

Adarmes AD, Almeria M, Alonso Losada MG, Alonso Cánovas A, Alonso Frech F, Alonso Redondo R, Álvarez I, Álvarez Saucó M, Aneiros Díaz A, Arnáiz S, Arribas S, Ascunce Vidondo A, Aguilar M, Ávila Rivera MA, Bernardo Lambrich N, Bejr-Kasem H, Blázquez Estrada M, Botí M, Borrue C, Buongiorno MT, Cabello González C, Cabo López I, Caballol N, Cámara Lorenzo A, Carrillo F, Carrillo Padilla FJ, Casas E, Catalán MJ, Clavero P, Cortina Fernández A, Cosgaya M, Cots Foraster A, Crespo Cuevas A, Cubo E, de Deus Fonticoba T, de Fábregues O, Díez-Fairen M, Erro E, Escalante S, Estelrich Peyret E, Fernández Guillán N, Gámez P, Gallego M, García Caldentey J, García Campos C, García Moreno JM, Gastón I, Guillén Fopiani D, Gómez Garre MP, Gómez Mayordomo V, González Aloy J, González-Aramburu I, González Ardura J, González García B, González Palmás MJ, González Toledo GR, Golpe Díaz A, Grau Solá M, Guardia G, Hernández Vara J, Horta-Barba A, Idoate Calderón

D, Infante J, Jesús S, Kulisevsky J, Kurtis M, Labandeira C, Labrador MA, Lacruz F, Lage Castro M, Legarda I, López Ariztegui N, López Díaz LM, López Manzanares L, López Seoane B, Lucas del Pozo S, Macías Y, Mata M, Martí Andres G, Martí MJ, Martínez Castrillo JC, Martínez-Martin P, McAfee D, Meitín MT, Menéndez González M, Méndez del Barrio C, Mir P, Miranda Santiago J, Morales Casado MI, Moreno Diéguez A, Nogueira V, Novo Amado A, Novo Ponte S, Ordás C, Pagonabarraga J, Pareés I, Pascual-Sedano B, Pastor P, Pérez Fuertes A, Pérez Noguera R, Planas-Ballvé A, Planellas LL, Prats MA, Prieto Jurczynska C, Puente V, Pueyo Morlans M, Redondo Rafeles N, Rodríguez Méndez L, Rodríguez Pérez AB, Roldán F, Ruíz De Arcos M, Ruíz Martínez J, Sánchez Alonso P, Sánchez-Carpintero M, Sánchez Díez G, Sánchez Rodríguez A, Santacruz P, Santos García D, Segundo Rodríguez JC, Seijo M, Sierra Peña M, Solano Vila B, Suárez Castro E, Tartari JP, Valero C, Vargas L, Vela L, Villanueva C, Vives B, Villar MD

Name (Last Name, First Name)	Location	Role	Contribution
Astrid Adarmes, Daniela	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
Almeria, Marta	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Neuropsychologist; evaluation of participants
Alonso Losada, María Gema	Hospital Álvaro Cunqueiro, Complejo Hospitalario Universitario de Vigo (CHUVI), Vigo, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Alonso Cánovas, Araceli	Hospital Universitario Ramón y Cajal, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Alonso Frech, Fernando	Hospital Universitario Clínico San Carlos, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Alonso Redondo, Ruben	Hospital Universitario Lucus Augusti (HULA), Lugo, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Aneiros Díaz, Ángel	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Álvarez, Ignacio	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Álvarez Saucó, María	Hospital General Universitario de Elche, Elche, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Arnáiz, Sandra	Complejo Asistencial Universitario de Burgos, Burgos, Spain	Site investigator	Evaluation of participants and/or data management
Arribas, Sonia	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Neuropsychologist; evaluation of participants
Ascunce Vidondo, Arancha	Complejo Hospitalario de Navarra, Pamplona, Spain	Site investigator	Evaluation of participants and/or data management

(Continued)

Name (Last Name, First Name)	Location	Role	Contribution
Aguilar, Miquel	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Ávila Rivera, Maria Asunción	Consorci Sanitari Integral, Hospital General de L'Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Bernardo Lambrich, Noemí	Hospital de Tortosa Verge de la Cinta (HTVC), Tortosa, Tarragona, Spain	Site investigator	Evaluation of participants and/or data management
Bejr-Kasem, Helena	Hospital de Sant Pau, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Blázquez Estrada, Marta	Hospital Universitario Central de Asturias, Oviedo, Spain	Site investigator	Evaluation of participants and/or data management
Botí González, Maria Ángeles	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Neuropsychologist; evaluation of participants
Borrué, Carmen	Hospital Infanta Sofía, Madrid, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Buongiorno, Maria Teresa	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Nurse study coordinator
Cabello González, Carolina	Complejo Hospitalario de Navarra, Pamplona, Spain	Site investigator	Scheduling of evaluations
Cabo López, Iria	Complejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Caballol, Nuria	Consorci Sanitari Integral, Hospital Moisès Broggi, Sant Joan Despí, Barcelona, Spain.	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Cámara Lorenzo, Ana	Hospital Clínic de Barcelona, Barcelona, Spain	Site investigator	Nurse study coordinator
Carrillo, Fátima	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
Carrillo Padilla, Francisco José	Hospital Universitario de Canarias, San Cristóbal de la Laguna, Santa Cruz de Tenerife, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Casas, Elena	Complejo Asistencial Universitario de Burgos, Burgos, Spain	Site investigator	Evaluation of participants and/or data management
Catalán, Maria José	Hospital Universitario Clínico San Carlos, Madrid, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Clavero, Pedro	Complejo Hospitalario de Navarra, Pamplona, Spain	Site investigator	Evaluation of participants and/or data management
Cortina Fernández, A	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Coordination of blood extractions
Cosgaya, Marina	Hospital Clínic de Barcelona, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Cots Foraster, Anna	Institut d'Assistència Sanitària (IAS) - Institutíu Cátala de la Salut. Girona, Spain	Site investigator	Evaluation of participants and/or data management
Crespo Cuevas, Ane	Hospital del Mar, Barcelona, Spain.	Site investigator	Evaluation of participants and/or data management
Cubo, Esther	Complejo Asistencial Universitario de Burgos, Burgos, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
De Deus Fonticoba, Teresa	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Nurse study coordinator Evaluation of participants and/or data management

(Continued)

Name (Last Name, First Name)	Location	Role	Contribution
De Fábregues, Oriol	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Díez Fairen, M	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Erro, Elena	Complejo Hospitalario de Navarra, Pamplona, Spain	Site investigator	Evaluation of participants and/or data management
Escalante, Sonia	Hospital de Tortosa Verge de la Cinta (HTVC), Tortosa, Tarragona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Estelrich Peyret, Elena	Institut d'Assistència Sanitària (IAS) - Institutí CÀtala de la Salut. Girona, Spain	Site investigator	Evaluation of participants and/or data management
Fernández Guillán, Noelia	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Neuroimaging studies
Gámez, Pedro	Complejo Asistencial Universitario de Burgos, Burgos, Spain	Site investigator	Evaluation of participants and/or data management
Gallego, Mercedes	Hospital La Princesa, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
García Caldentey, Juan	Centro Neurológico Oms 42, Palma de Mallorca, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
García Campos, Cristina	Hospital Universitario Virgen Macarena, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
García Moreno, Jose Manuel	Hospital Universitario Virgen Macarena, Sevilla, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Gastón, Itziar	Complejo Hospitalario de Navarra, Pamplona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Guillén Fopiani, Desiré	Complejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain	Site investigator	Neuropsychologist; evaluation of participants
Gómez Garre, María del Pilar	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Genetic studies coordination
Gómez Mayordomo, Víctor	Hospital Clínico San Carlos, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
González Aloy, Javier	Institut d'Assistència Sanitària (IAS) - Institutí CÀtala de la Salut. Girona, Spain	Site investigator	Evaluation of participants and/or data management
González Aramburu, Isabel	Hospital Universitario Marqués de Valdecilla, Santander, Spain	Site investigator	Evaluation of participants and/or data management
González Ardura, Jessica	Hospital Universitario Lucus Augusti (HULA), Lugo, Spain	Site investigator	Evaluation of participants and/or data management
González García, Beatriz	Hospital La Princesa, Madrid, Spain	Site investigator	Nurse study coordinator
González Palmás, María Josefa	Complejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain	Site investigator	Evaluation of participants and/or data management
González Toledo, Gabriel Ricardo	Hospital Universitario de Canarias, San Cristóbal de la Laguna, Santa Cruz de Tenerife, Spain	Site investigator	Evaluation of participants and/or data management
Golpe Díaz, Ana	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Laboratory analysis coordination
Grau Solá, Mireia	Consorci Sanitari Integral, Hospital Moisès Broggi, Sant Joan Despí, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Guardia, Gemma	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management

(Continued)

Name (Last Name, First Name)	Location	Role	Contribution
Hernández Vara, Jorge	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Horta Barba, Andrea	Hospital de Sant Pau, Barcelona, Spain	Site investigator	Neuropsychologist; evaluation of participants
Idoate Calderón, Daniel	Complejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain	Site investigaor	neuropsychologist; evaluation of participants
Infante, Jon	Hospital Universitario Marqués de Valdecilla, Santander, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Jesús, Silvia	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
Kulisevsky, Jaime	Hospital de Sant Pau, Barcelona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Kurtis, Mónica	Hospital Ruber Internacional, Madrid, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Labandeira, Carmen	Hospital Álvaro Cunqueiro, Complejo Hospitalario Universitario de Vigo (CHUVI), Vigo, Spain	Site investigator	Evaluation of participants and/or data management
Labrador Espinosa, Miguel Ángel	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Neuroimaging data analysis
Lacruz, Francisco	Complejo Hospitalario de Navarra, Pamplona, Spain	Site investigator	Evaluation of participants and/or data management
Lage Castro, Melva	Complejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain	Site investigator	Evaluation of participants and/or data management
Legarda, Inés	Hospital Universitario Son Espases, Palma de Mallorca, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
López Ariztegui, Nuria	Complejo Hospitalario de Toledo, Toledo, Spain	Site investigator / PI	Evaluation of participants and/or data management
López Díaz, Luis Manuel	Hospital Da Costa de Burela, Lugo, Spain	Site investigator	Evaluation of participants and/or data management
López Manzanares, Lydia	Hospital La Princesa, Madrid, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
López Seoane, Balbino	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Neuroimaging studies
Lucas del Pozo, Sara	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Macías, Yolanda	Fundación Hospital de Alcorcón, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Mata, Marina	Hospital Infanta Sofía, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Martí Andres, Gloria	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Martí, Maria José	Hospital Clínic de Barcelona, Barcelona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Martínez Castrillo, Juan Carlos	Hospital Universitario Ramón y Cajal, Madrid, Spain	Site investigator /PI	Coordination at the center Evaluation of participants and/or data management
Martinez-Martin, Pablo	Centro Nacional de Epidemiología y CIBERNED, Instituto de Salud Carlos III. Madrid	Collaborator in statistical and methods analysis	Methods and statistical reviewer
McAfee, Darrian	University of Pennsylvania, Philadelphia	Collaborator in english style	English style reviewer

(Continued)

Name (Last Name, First Name)	Location	Role	Contribution
Meitín, María Teresa	Hospital Da Costa de Burela, Lugo, Spain	Site investigator	Evaluation of participants and/or data management
Menéndez González, Manuel	Hospital Universitario Central de Asturias, Oviedo, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Méndez del Barrio, Carlota	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
Mir, Pablo	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Miranda Santiago, Javier	Complejo Asistencial Universitario de Burgos, Burgos, Spain	Site investigator	Evaluation of participants and/or data management
Morales Casado, María Isabel	Complejo Hospitalario de Toledo, Toledo, Spain.	Site investigator	Evaluation of participants and/or data management
Moreno Diéguez, Antonio	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Neuroimaging studies
Nogueira, Víctor	Hospital Da Costa de Burela, Lugo, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Novo Amado, Alba	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Neuroimaging studies
Novo Ponte, Sabela	Hospital Universitario Puerta de Hierro, Madrid, Spain.	Site investigator	Evaluation of participants and/or data management
Ordás, Carlos	Hospital Rey Juan Carlos, Madrid, Spain, Madrid, Spain.	Site Investigator	Evaluation of participants and/or data management
Pagonabarraga, Javier	Hospital de Sant Pau, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Isabel Pareés	Hospital Ruber Internacional, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Pascual-Sedano, Berta	Hospital de Sant Pau, Barcelona, Spain	Site Investigator	Evaluation of participants and/or data management
Pastor, Pau	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Pérez Fuertes, Aída	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Blood analysis
Pérez Noguera, Rafael	Hospital Universitario Virgen Macarena, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
Planas-Ballvé, Ana	Consorci Sanitari Integral, Hospital Moisès Broggi, Sant Joan Despí, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Planellas, Lluís	Hospital Clínic de Barcelona, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Prats, Marian Ángeles	Institut d'Assistència Sanitària (IAS) - Institutí Cátala de la Salut. Girona, Spain	Site investigator	Evaluation of participants and/or data management
Prieto Jurczynska, Cristina	Hospital Rey Juan Carlos, Madrid, Spain, Madrid, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Puente, Víctor	Hospital del Mar, Barcelona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Pueyo Morlans, Mercedes	Hospital Universitario de Canarias, San Cristóbal de la Laguna, Santa Cruz de Tenerife, Spain	Site investigator	Evaluation of participants and/or data management
Redondo, Nuria	Hospital La Princesa, Madrid, Spain	Site Investigator	Evaluation of participants and/or data management

(Continued)

Name (Last Name, First Name)	Location	Role	Contribution
Rodríguez Méndez, Luisa	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Blood analysis
Rodríguez Pérez, Amparo Belén	Hospital General Universitario de Elche, Elche, Spain	Site investigator	Evaluation of participants and/or data management
Roldán, Florinda	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Neuroimaging studies
Ruíz de Arcos, María	Hospital Universitario Virgen Macarena, Sevilla, Spain.	Site investigator	Evaluation of participants and/or data management
Ruíz Martínez, Javier	Hospital Universitario Donostia, San Sebastián, Spain	Site investigator	Evaluation of participants and/or data management
Sánchez Alonso, Pilar	Hospital Universitario Puerta de Hierro, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Sánchez-Carpintero, Macarena	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Neuroimaging studies
Sánchez Díez, Gema	Hospital Universitario Ramón y Cajal, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Sánchez Rodríguez, Antonio	Hospital Universitario Marqués de Valdecilla, Santander, Spain	Site investigator	Evaluation of participants and/or data management
Santacruz, Pilar	Hospital Clínic de Barcelona, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Santos García, Diego	CHUAC, Complejo Hospitalario Universitario de A Coruña	Coordinator of the Project	Coordination of the COPPADIS-2015
Segundo Rodríguez, José Clemente	Complejo Hospitalario de Toledo, Toledo, Spain	Site investigator	Evaluation of participants and/or data management
Seijo, Manuel	Complejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Sierra, María	Hospital Universitario Marqués de Valdecilla, Santander, Spain	Site investigator	Evaluation of participants and/or data management
Solano, Berta	Institut d'Assistència Sanitària (IAS) - Institut Càtala de la Salut. Girona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Suárez Castro, Ester	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, A Coruña, Spain	Site investigator	Evaluation of participants and/or data management
Tartari, Juan Pablo	Hospital Universitari Mutua de Terrassa, Terrassa, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Valero, Caridad	Hospital Arnau de Vilanova, Valencia, Spain	Site investigator	Evaluation of participants and/or data management
Vargas, Laura	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
Vela, Lydia	Fundación Hospital de Alcorcón, Madrid, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Villanueva, Clara	Hospital Universitario Clínico San Carlos, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Vives, Bárbara	Hospital Universitario Son Espases, Palma de Mallorca, Spain	Site investigator	Evaluation of participants and/or data management
Villar, Maria Dolores	Hospital Universitario de Canarias, San Cristóbal de la Laguna, Santa Cruz de Tenerife, Spain	Site investigator	Evaluation of participants and/or data management