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Research Report

Staging Parkinson's Disease According to the MNCD (Motor/Non-motor/Cognition/Dependency) Classification Correlates with Disease Severity and Quality of Life

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Abstract.
Background: Recently, a novel simple classification called MNCD, based on 4 axes (Motor; Non-motor; Cognition; Dependency) and 5 stages, has been proposed to classify Parkinson's disease (PD).
Objective: Our aim was to apply the MNCD classification in a cohort of PD patients for the first time and also to analyze the correlation with quality of life (QoL) and disease severity.
Methods: Data from the baseline visit of PD patients recruited from 35 centers in Spain from the COPPADIS cohort from January 2016 to November 2017 were used to apply the MNCD classification. Three instruments were used to assess QoL: 1) the 39-item Parkinson's disease Questionnaire [PDQ-39]); PQ-10; the EUROHIS-QOL 8-item index (EUROHIS-QOL8).
Results: Four hundred and thirty-nine PD patients (62.05 ± 7.84 years old; 59% males) were included. MNCD stage was: stage 1, 8.4% (N = 37); stage 2, 62% (N = 272); stage 3, 28.2% (N = 124); stage 4-5, 1.4% (N = 6). A more advanced MNCD stage was associated with a higher score on the PDQ39SI ($p < 0.0001$) and a lower score on the PQ-10 ($p < 0.0001$) and EUROHIS-QOL8 ($p < 0.0001$). In many other aspects of the disease, such as disease duration, levodopa equivalent

daily dose, motor symptoms, non-motor symptoms, and autonomy for activities of daily living, an association between the stage and severity was observed, with data indicating a progressive worsening related to disease progression throughout the proposed stages.

Conclusion: Staging PD according to the MNCD classification correlated with QoL and disease severity. The MNCD could be a proper tool to monitor the progression of PD.

Keywords: Axial symptoms, cognition, MNCD classification, non-motor symptoms, Parkinson's disease, quality of life

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder causing not only motor but also and non-motor symptoms (NMS) that result in loss of patient autonomy for activities of daily living (ADL) and quality of life (QoL) [1]. Since there is currently no cure for PD, the management is centered around the patient's symptoms, aiming to provide the best possible QoL [2]. Therefore, QoL is a key factor to measure the impact that the disease has on the patient over time [3]. In the context of a clinically heterogeneous neurodegenerative disorder like PD, simple classifications that adequately inform clinicians about key symptoms at different stages of the disease would be crucial. Recently, a novel yet simple classification called MNCD has been proposed [4]. The MNCD is based on 4 axes: M, Motor; N, Non-motor; C, Cognition; D, Dependency. Motor and Non-motor axes include 4 sub-axes: "Motor fluctuations", "Dyskinesia", "Axial symptoms", and "Tremor" for the Motor axis; "Neuropsychiatric symptoms", "Autonomic dysfunction", "Sleep disturbances and fatigue", "Pain and sensory disorders" for the Non-motor axis. Regarding Cognition and Dependency, patients can be classified as with normal cognition, mild cognitive impairment, or dementia, and with independence for ADL, dependency for instrumental ADL, or dependency for basic ADL, respectively. According to the MNCD, 5 stages are considered, from stage 1 (no disabling motor symptoms or NMS with normal cognition and independency for ADL) to 5 (dementia and dependency for basic ADL) [4]. In summary, the MNCD classification includes 4 major axes and 5 stages to identify key symptoms and monitor the progression of PD. Importantly, this is the first classification that takes into account key aspects of the PD such as axial symptoms, NMS, cognition and autonomy for ADL, due to their prognostic value, their impact on the patient and/or caregiver and/or their importance when deciding on a specific therapeutic attitude. Currently, the MNCD classification is a proof of concept and a study to examine the usability and variability of this tool in PD patients is on-going.

The objective of this study was to apply the MNCD classification in a cohort of patients with PD for the first time. Data were obtained from the COPPADIS cohort [5] and the criteria to apply over the data for different symptoms included in the MNCD classification were specifically defined. Our hypothesis was that patients' QoL would be different between the different PD stages according to the MNCD classification, with a better QoL in stage 1 and a worse QoL at a higher advanced stage (i.e., a more advanced MNCD stage, a worse QoL). In other words, we wanted to know if the MNCD stage can be a good indicator of PD patient's QoL. In addition, we analyzed disease severity regarding to the MNCD stage.

MATERIALS AND METHODS

Data from PD patients recruited from 35 hospitals in Spain from the COPPADIS cohort [5] from January 2016 to November 2017 were used in this study. Methodology about COPPADIS-2015 study can be consulted at https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-016-0548-9 [6]. This is a multi-center, observational, 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 [7]. Exclusion criteria were: non-PD parkinsonism, dementia (Mini-Mental State Examination <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), and the presence of comorbidity, sequelae, or any disorder that could interfere with the assessment. For the present specific transversal and retrospective analysis, data from the baseline visit were used to apply the MNCD classification (axes and stages).

PD patient assessment

Information on sociodemographic aspects, factors related to PD, comorbidity, and treatment including levodopa equivalent daily dose (LEDD) [8] were collected at baseline. The evaluation included (1) motor assessment (Hoenh & Yahr [H&Y], Unified Parkinson's Disease Rating Scale [UPDRS] part III and part IV, Freezing of Gait Questionnaire [FOGQ]), (2) NMS (Non-Motor Symptoms Scale [NMSS], Parkinson's Disease Sleep Scale [PDSS], Visual Analog Scale-Pain [VAS-Pain], Visual Analog Fatigue Scale [VAFS]), (3) cognition (Parkinson´s Disease Cognitive Rating Scale [PD-CRS]), (4) 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]), (5) disability (Schwab and England Activities of daily living Scale [ADLS]), and (6) health-related (the 39-item Parkinson's disease Questionnaire [PDQ-39]) and global QoL (PQ-10, the EUROHIS-QOL 8-item index [EUROHIS-QOL8]) [6]. In all the questionnaires/scales a higher score indicates a more severe affectation apart from PDSS, PD-CRS, ADLS, and EUROHIS-QOL8, which were the opposite. In patients with motor fluctuations, the motor evaluation was made during the OFF state (without medication in the last 12 h) and during the ON state whereas in patients without motor fluctuations, it was conducted without medication. The non-motor assessment was conducted after taking dopaminergic medication.

Three different instruments were used to assess QoL: 1) PDQ-39 [9], 2) a rating of global perceived QoL (PQ-10) on a scale from 0 (worst) to 10 (best) [10], and 3) EUROHIS-QOL8 [11]. The PDQ-39 is a questionnaire to assess specifically the patients' health-related quality of life (HRQoL) in PD patients. It has 39 items grouped into 8 domains: (1) Mobility (items 1 to 10); (2) Activities of daily living (items 11 to 16); (3) Emotional well-being (items 17 to 22); (4) Stigma (items 23 to 26); (5) Social support (items 27 to 29); (6) Cognition (items 30 to 33); (7) Communication (items 34 to 36); (8) Pain and discomfort (items 37 to 39). For each item, the score may range from 0 (never) to 4 (always). The symptoms refer to the 4 weeks prior to assessment. Domain total scores are expressed as a percentage of the corresponding maximum possible score and a Summary Index is obtained as average of the domain scores (PDQ-39SI). The EUROHIS-QOL8 is an 8-item GQoL questionnaire (quality of life; health status; energy; autonomy for activities of daily living; self-esteem; social relationships; economic capacity; habitat) derived from the WHOQOL-BREF. For each item, the score ranges from 0 (not at all) to 5 (completely). The total score is expressed as the mean of the individual scores. A higher score indicates a better QoL.

MNCD classification

The MNCD classification has been designed with the idea that it can be applied by a neurologist in his/her clinical practice based on the symptoms detected with the anamnesis and examination and without the need to use specific scales, being the neurologist who scores the presence or absence of symptoms based on to whether they produce a truly significant impact on the patient (e.g., it is not the same dysthymia or minor depression than major depression). For this study, we defined the symptoms specifically according all the information collected from the patients from the COPPADIS cohort (Table 1).

Regarding the axes, patients were classified for each axis in groups [4]. For axis 1 (Motor): M_0 (no sub-axis with symptoms); M_1 (1 sub-axis with symptoms); M_2 (2 sub-axes with symptoms); M_3 (3 sub-axes with symptoms); M_4 (all sub-axes with symptoms). For axis 2 (Non-motor): N_0 (no sub-axis with symptoms); N_1 (1 sub-axis with symptoms); N_2 (2 sub-axes with symptoms); N_3 (3 sub-axes with symptoms); N_4 (all sub-axes with symptoms). For axis 3 (Cognition): C_0, normal cognition; C_1, mild cognitive impairment; C_2, dementia. For axis 4, D_0 (independency for ADL); D_1 (dependency for instrumental ADL); D_2 (dependency for basic ADL). A total sum (MNCD total score) was calculated with a range from 0 ($M_0N_0C_0D_0$) to 12 ($M_4N_4C_2D_2$).

Because the COPPADIS cohort includes a smaller number of advanced PD patients, patients with a MNCD stage 4 or 5 were included in the same category. MNCD stages [4] were: 1) Stage 1, if the patient has no any relevant motor and NMS, being independent for ADL and without cognitive impairment; 2) Stage 2, if there is at least 1 motor symptom or 1 NMS scoring in the MNCD classification, but there is neither cognitive impairment nor dependency for ADL; 3) Stage 3, if there is mild cognitive impairment (C = 1) and/or dependency for instrumental ADL (D = 1) and the score on axes 1 (Motor) and 2 (Non-Motor) could be from 0 to 4; Stage 4-5, if there is dementia (C = 2) and/or dependency for basic ADL (D = 2).

Table 1
Criteria for symptoms defined as clinically relevant symptoms in this study according to the MNCD classification; 0, the symptom is not present or if it is present is no clinically relevant; 1, the symptom is present and it is clinically relevant

MOTOR SYMPTOMS
⟶**M1, Motor fluctuations.** UPDRS-IV-item 39; 0 = 0 (no OFF time); from 1 (OFF time 1-2% of the waking day) to 4 (OFF time 76-100% of the waking day) = 1.
⟶**M2, Dyskinesia.** UPDRS-IV-item 33; 0 = 0 (not disabling dyskinesia); from 1 (mildly disabling dyskinesia) to 4 (completely disabled dyskinesia) = 1.
⟶**M3, Axial symptoms:**
***M3A, Dysphagia**. NMSS-item 20; from 0 (absent) to 2 (often –l1/week– but mild or moderate but rarely –<1/week) = 0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe) = 1.
***M3B, Hypomimia.** UPDRS-III-item 19; from 0 (normal) to 3 (moderate hypomimia; lips parted some of the time) = 0; 4 (masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more) = 1.
***M3C, FOG.** FOGQ-item 3; from 0 (never) to 2 (rarely –about 1/week) = 0; from 3 (often –about 1/day) to 4 (always –about every time while walking) = 1.
***M3D, Falls.** UPDRS-II-item 13; from 0 (none) to 1 (rare falling) = 0; from 2 (occasionally falls, less than once per day) to 4 (falls more than once daily) = 1.
***M3E, Abnormal posture.** UPDRS-III-item 28; from 0 (normal erect) to 2 (moderately stooped posture, definitely abnormal; can be slightly leaning to one side) = 0; from 3 (severely stooped posture with kyphosis; can be moderately leaning to one side) to 4 (marked flexion with extreme abnormality of posture) = 1.
***M3F, Postural instability.** UPDRS-III-item 30; from 0 (normal) to 1 (retropulsion, but recovers unaided) = 0; from 2 (absence of postural response; would fall if not caught by examiner) to 4 (unable to stand without assistance) = 1.
***M3G, Gait problems.** UPDRS-II-item 15; from 0 (normal) to 2 (moderate difficulty, but requires little or no assistance) = 0; from 3 (severe disturbance of walking, requiring assistance) to 4 (cannot walk at all, even with assistance) = 1.
⟶**M4, Tremor.** UPDRS-II-item 16, from 0 (absent) to 2 (moderate; bothersome to patient) = 0; from 3 (severe; interferes with many activities) to 4 (marked; interferes with most activities) = 1.
NON-MOTOR SYMPTOMS
⟶**N1, Neuropsychiatric symptoms:**
***N1A, Major depression.** No major depression = 0; major depression (DSM – V criteria [38])=1.
***N1B, Anxiety.** NMSS-item 9; from 0 (absent) to 2 (often –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.
***N1C, ICD and/or CB.** Previously published cutoff points of the QUIP-RS were applied to define the case as 1: gambling ≥6, buying ≥8, sex ≥8, eating ≥7, hobbyism-punding ≥7 [39].
***N1D, Apathy.** NPI-item G; from 0 (absent) to 2 (sometimes –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.
***N1E, Delusions.** NPI-item A; from 0 (absent) to 2 (sometimes –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.
***N1F, Hallucinations.** NPI-item B; from 0 (absent) to 2 (sometimes –1/week– – but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.
***N1G, Agitation.** NPI-item C; from 0 (absent) to 2 (sometimes –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.

(*Continued*)

⟶**N2, Autonomic dysfunction:**

***N2A, Orthostatic dizziness.** NMSS-item 1; from 0 (absent) to 2 (often –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.

***N2B, Syncope.** NMSS-item 2; from 0 (absent) to 2 (often –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.

***N2C, Sweating.** NMSS-item 30; from 0 (absent) to 2 (often –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.

⟶**N3, Sleep disturbances and fatigue:**

***N3A, Sleep disturbances.** Previously published cutoff points of the PDSS were applied to define the case as 1: an overall score below 82 or a score below 5 on at least one item [40].

***N3B, Fatigue.** NMSS-item 4; from 0 (absent) to 2 (often –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.

⟶**N4, Pain and sensory disorders:**

***N4A, Pain.** NMSS-item 27; from 0 (absent) to 2 (often –1/week– but mild or moderate but rarely –<1/week)=0; from 3 (rarely but severe or mild but frequent –several times per week) to 12 (very frequent –daily or all the time– and severe)=1.

***N4B, Cramps and/or spasms.** PDQ-39-item 37; from 0 (never) to 2 (sometimes)=0; from 3 (often) to 4 (always)=1.

***N4C, Unpleasant hot or cold feeling.** PDQ-39-item 39; from 0 (never) to 2 (sometimes)=0; from 3 (often) to 4 (always)=1.

COGNITION

⟶**C_0, normal cognition.** PD-CRS total score ≥81.

C_1, mild cognitive impairment. PD-CRS total score <81 and >64.

C_2, dementia. PD-CRS total score ≤64 and dependency for basic ADL (ADLS ≤50).*

*Patients with PD-CRS ≤64 but ADLS >50 were classified as C_1.

DEPENDENCY

⟶**D_0, independence for ADL.** ADLS ≥80.

D_1, dependency for instrumental ADL. ADLS >50 and <80.

D_2, dependency for basic ADL. ADLS ≤50.

ADL, activities of daily living; ADLS, Schwab and England Activities of daily living Scale; CB, compulsive behavior; FOG, freezing of gait; FOGQ, Freezing of Gait Questionnaire; ICD, impulse control disorder; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson´s disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDQ-39, 39-item Parkinson's disease Questionnaire; PDSS, Parkinson's Disease Sleep Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Data analysis

Data were processed using SPSS 20.0 for Windows. For comparison of QoL and other disease related variables between patients with a different MNCD stage (all stages together or two consecutive stages), the Student's *t*-test, Mann-Whitney U test, Chi-square test, Fisher test, ANOVA test, or Kuskal-Wallis tes were used as appropriate (distribution for variables was verified by one-sample Kolmogorov-Smirnov test). Spearman's or Pearson's correlation coefficient, as appropriate, were used for analyzing the relationship between the MNCD total score (from 0 to 12) and PDQ-39SI, EUROHIS-QOL8 and PQ-10 scores. Correlations were considered weak for coefficient values $\leq$0.29, moderate for values between 0.30 and 0.59, and strong for values $\geq$0.60.

Standard protocol approvals, registrations, and patient consents

We received approval from the *Comité de Ética de la Investigación Clínica de Galicia* (2014/534; 02/DEC/2014) and a written informed consent from all participants in this study was obtained. 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. Deidentified participant data are not available for legal and ethical reasons.

RESULTS

The study included 439 PD patients (62.05 $\pm$ 7.84 years old; 59% males). Mean disease duration (year from symptoms onset) was 5.73 $\pm$ 4.39, and only 10% of the patients had H&Y stage from 3 to 5. Up to 43.7% and 89.1% of the patients had at least one clinically relevant motor symptom (33.3% motor fluctuations; 7.5% disabling dyskinesia; 18% axial symptoms; 5.2% tremor) and NMS (49% neuropsychiatric symptoms; 31% autonomic dysfunction; 78.6% sleep disturbances and/or fatigue; 31.9% pain and sensory disorders), respectively (Table 2, Fig. 1A). Of axial symptoms, dysphagia was the most frequent (10%), whereas sleep disturbances (72%), fatigue (36%), and anxiety (23.7%) were the most frequent NMS. Of 439 PD patients, 111 (25.3%) had mild cognitive impairment, and only 1 patient had dementia. Regarding dependency for ADL, 41 (9.3%) were dependent for instrumental ADL and only 6 (1.4%) for basic ADL. Up to 56.3% of the patients didn't suffer from any clinically relevant motor symptom (classified as M_0) compared to only 10.9% with regard to NMS (N_0) (Fig. 1B). Only 1 patient had relevant motor symptoms related to all sub-axes from axis 1 (motor fluctuations + dyskinesia + axial symptoms + tremor) (M_4) compared to 51 patients with symptoms related to all sub-

Table 2
Frequency of patients presenting with clinically relevant symptoms collected according to the MNCD classification (N = 439).

	%
MOTOR SYMPTOMS	43.7
Motor fluctuations	33.3
Dyskinesia	7.5
Axial symptoms	18
-Dysphagia	10
-Hypomimia	0
-FOG	5.9
-Falls	5
-Abnormal posture	2.7
-Postural instability	2.7
-Gait problems	3
Tremor	5.2
NON-MOTOR SYMPTOMS	89.1
Neuropsychiatric symptoms	49
-Major depression	16.9
-Anxiety	23.7
-ICD and/or CB	18
-Apathy	15.7
-Delusions	2.7
-Hallucinations	3
-Agitation	4.8
Autonomic dysfunction	31
-Orthostatic dizziness	17.5
-Syncope	0.2
-Sweating	18.2
Sleep disturbances and fatigue	78.6
-Sleep disturbances	72
-Fatigue	36
Pain and sensory disorders	31.9
-Pain	18.7
-Cramps and/or spasms	13.4
-Unpleasant hot or cold feeling	11.8
COGNITION	
Normal	74.5
Mild cognitive impairment	25.3
Dementia	0.2
DEPENDENCY	
Independence for ADL	89.3
Dependency for instrument ADL	9.3
Dependency for basic ADL	1.4

The results represent percentage. ADL, activities of daily living; CB, compulsive behavior; FOG, freezing of gait; ICD, impulse control disorder.

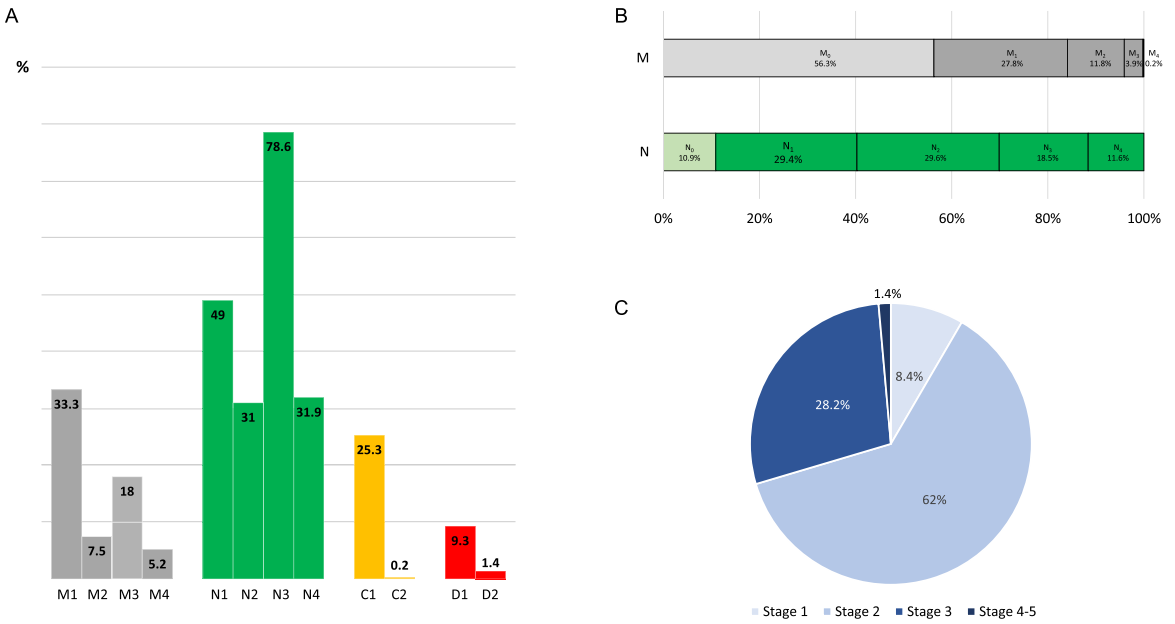

Fig. 1. A) Frequency of patients with clinically relevant motor symptoms, NMS, cognitive problems and dependency for ADL according to the MNCD classification (M1, Motor fluctuations; M2, Dyskinesia; M3, Axial symptoms; M4, Tremor; N1, Neuropsychiatric symptoms; N2, Autonomic dysfunction; N3, Sleep disturbances and/or fatigue; N4, Pain and sensory disorders; C1, Mild cognitive impairment; C2, Dementia; D1, Dependency for instrumental ADL; D2, Dependency for basic ADL). B) Frequency of patients classified as M_0, M_1, M_2, M_3, M_4 and N_0, N_1, N_2, N_3 and N_4. C) Frequency of different stages of the MNCD classification.

axes from axis 2 (N_4) (neuropsychiatric symptoms + autonomic dysfunction + sleep disturbances and/or fatigue + pain and sensory disorders). Regarding MNCD stages (Fig. 1C), the distribution was; stage 1, 8.4% (N = 37); stage 2, 62% (N = 272); stage 3, 28.2% (N = 124); stage 4-5, 1.4% (N = 6; 5 patients with a stage 4 and only 1 patient with a stage 5 from the MNCD classification according to the original description [4]).

A more advanced MNCD stage was associated with a longer disease duration ($p = 0.001$), to be older ($p < 0.0001$), a higher LEDD and number of non-antiparkinsonian drugs ($p < 0.0001$), and a worse status in terms of motor symptoms (H&Y; UPDRS-III; UPDRS-IV; FOGQ; $p < 0.0001$ for all analysis), NMS (PD-CRS, NMSS, BDI-II, NPI, PDSS, VAS-PAIN, VASF – physical, VASF – mental; $p < 0.0001$ for all analysis), and autonomy for ADL ($p < 0.0001$) (Table 3). Regarding QoL, both health-related and global QoL were related to the MNCD stage, such that the more advanced MNCD stage correlated to a higher score on the PDQ39SI and a lower score on the PQ-10 and the EUROHIS-QOL8 (Table 4). Considering the four MNCD stages (stage 1 vs stage 2 vs stage 3 vs stage 4-5), differences were significant in the three scales used to assess QoL: PDQ-39SI, 6.65 ± 4.27 vs. 15.5 ± 11.24 vs. 23.8 ± 16.14 vs. 46.36 ± 11.67 ($p < 0.0001$); PQ-10, 8 ± 1.38 vs. 7.41 ± 1.42 vs. 6.65 ± 1.8 vs. 5.17 ± 2.78 ($p < 0.0001$); EUROHIS-QOL8, 4.18 ± 0.39 vs. 3.83 ± 0.52 vs. 3.54 ± 0.58 vs. 3.12 ± 0.5 ($p < 0.0001$) (Table 4, Fig. 2A). By domains, significant differences were observed in all domains between groups when all the stages (from stage 1 to stage 4-5) were considered except in stigmatization (PDQ-39) and social relationships and habitat (EUROHIS-QOL8) (Table 4, Fig. 2B). When a MNCD stage was compared with its next consecutive stage, significant differences were detected in all comparisons for the PDQ-39SI: stage 1 vs. stage 2 ($p < 0.0001$); stage 2 vs. stage 3 ($p < 0.0001$); stage 3 vs. stage 4 ($p = 0.002$). For the PQ-10 and EUROHIS-QOL8, the only results that were not significant occurred when QoL in stage 3 was compared to QoL in stage 4 (Table 4).

Finally, a strong positive correlation was observed between the MNCD total score and the PDQ-39SI ($r = 0.693$; $p < 0.0001$). Moderate negative correlations were detected between the MNCD total score and the PQ-10 score ($r = -0.425$; $p < 0.0001$) and the EUROHIS-QOL8 total score ($r = -0.504$; $p < 0.0001$).

Table 3
Disease related characteristics, motor and non-motor symptoms, autonomy for activities of daily living and quality of life in PD patients with different stage according to the MNCD classification (N = 439)

	Stage 1 (N = 37)	Stage 2 (N = 272)	Stage 3 (N = 124)	Stage 4-5 (N = 6)	Total (N = 439)	*p*
Age	61.84 ± 7.45	59.8 ± 9.61	67.01 ± 7.32	63.33 ± 7.47	62.05 ± 7.84	<0.0001
Males (%)	56.8	60.7	55.6	66.7	59	0.775
Weight (kg)	77.51 ± 16.28	75.62 ± 13.91	76.74 ± 12.41	70.41 ± 10.08	76.02 ± 13.67	0.716
Disease duration (y)	4.06 ± 3.43	5.4 ± 3.81	6.73 ± 5.41	9.8 ± 5.4	5.73 ± 4.39	0.003
Antiparkinsonian drugs:						
- Levodopa	45.9	67.6	83.1	83.3	70.4	<0.0001
- Dopamine agonist	67.6	71.7	65.3	66.7	69.5	0.115
- MAO-B inhibitor	75.7	76.8	64.5	50	72.9	0.016
- COMT inhibitor	5.4	18.4	24.2	50	19.4	0.002
- Amantadine	5.4	8.8	11.3	16.7	9.3	0.099
L-dopa eq. daily dose (mg)	356.97 ± 276.78	540.01 ± 388.36	674.71 ± 441.8	1057.2 ± 762.12	569.48 ± 413.15	<0.0001
Number of non antip. Drugs	1 [0, 3]	2 [1, 3]	3 [1, 5.5]	3 [1, 6]	1 [0, 3]	<0.0001
Motor phenotype (%)						0.252
- Tremoric dominant	45.9	44.9	38.7	0	42.6	
- PIGD	37.8	39.7	48.4	83.3	42.6	
- Indeterminate	16.2	15.4	12.9	16.7	14.8	
Hoehn & Yahr - OFF	2 [1.5, 2]	2 [1.5, 2]	2 [2, 2.5]	3.5 [2, 4]	2 [2, 2]	<0.0001
- Stage from 3 to 5 (%)	0	7.8	15.6	60	10	<0.0001
UPDRS-III – OFF	16.94 ± 6.87	21.88 ± 11.01	26.24 ± 11.99	39.17 ± 13.51	22.97 ± 11.49	<0.0001
UPDRS-IV	0.43 ± 0.6	1.91 ± 2.17	2.67 ± 2.76	6 ± 3.95	2.06 ± 2.41	<0.0001
- Motor fluctuations (%)	0	31.2	45.2	83.3	33.3	<0.0001
- Dyskinesia (%)	0	7.4	8.9	33.3	7.5	0.024
FOGQ	0.95 ± 1.29	3.2 ± 3.96	5.62 ± 5.15	16.83 ± 4.07	3.87 ± 4.65	<0.0001
- Patients with FOG (%)	0	4.4	8.1	66.7	5.9	<0.0001
- Patients with falls (%)	0	1.5	12.1	50	5	<0.0001

(*Continued*)

Table 3
(*Continued*)

	Stage 1 (N = 37)	Stage 2 (N = 272)	Stage 3 (N = 124)	Stage 4-5 (N = 6)	Total (N = 439)	*p*
PD-CRS total score	98.62 ± 10.71	99.34 ± 11.72	73.66 ± 11.87	73.17 ± 11.91	91.67 ± 16.51	<0.0001
NMSS	12.54 ± 10.39	42.82 ± 32.94	60.77 ± 40.73	76.33 ± 43.98	45.79 ± 36.65	<0.0001
BDI-II	3.14 ± 2.93	8.32 ± 6.97	13.09 ± 8.49	16.5 ± 8.59	9.34 ± 7.77	<0.0001
- Major depression (%)	0	13.6	27.4	50	16.9	<0.0001
NPI	1.77 ± 2.94	5.48 ± 7.25	9.24 ± 9.99	7.17 ± 6.71	6.27 ± 8.16	<0.0001
QUIP-RS	1.24 ± 3.57	5.16 ± 9.31	4.25 ± 8.02	3.5 ± 8.57	4.55 ± 8.65	0.015
- ICD and/or CB (%)	0	20.2	18.5	16.7	18	0.028
PDSS	139.82 ± 9.52	112.26 ± 27.62	108.53 ± 24.68	82.33 ± 34.78	113.12 ± 27.28	<0.0001
VAS-PAIN	1.08 ± 2.24	2.61 ± 2.86	3.48 ± 3.34	5.19 ± 3.02	3.15 ± 2.83	<0.0001
VASF – physical	0.93 ± 1.7	3.02 ± 2.74	3.91 ± 2.84	6.86 ± 2.98	3.15 ± 2.83	<0.0001
VASF – mental	0.63 ± 1.13	2.21 ± 2.61	2.72 ± 2.86	3.66 ± 2.67	2.24 ± 2.65	<0.0001
ADLS	94.05 ± 4.97	90.73 ± 6.72	82.41 ± 12.77	41.66 ± 11.69	87.99 ± 11.1	<0.0001
PDQ-39SI	6.65 ± 4.27	15.5 ± 11.24	23.8 ± 16.14	46.36 ± 11.67	17.52 ± 13.76	<0.0001
EUROHIS-QOL8	4.18 ± 0.39	3.83 ± 0.52	3.54 ± 0.58	3.12 ± 0.5	3.76 ± 0.56	<0.0001
PQ-10	8.08 ± 1.38	7.41 ± 1.42	6.65 ± 1.8	5.17 ± 2.78	7.22 ± 1.63	<0.0001

The results represent percentages, mean ± SD or median [p25, p75]. Chi-squared, ANOVA and/or Kruskal-Wallis test were applied. Data about H&Y and UPDRS-III are during the OFF state (first thing in the morning without taking medication in the previous 12 h). ADLS, Schwab and England Activities of daily living Scale; BDI-II, Beck Depression Inventory-II; COMT, catechol-O-methyltransferase; CB, compulsive behavior; EUROHIS-QOL8, EUROHIS-QOL 8-item index; FOGQ, Freezing of Gait Questionnaire; ICD, impulse control disorder; MAO-B, Monoamine oxidase-B; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PD, Parkinson´s disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDQ-39, 39-item Parkinson's disease Questionnaire; PDSS, Parkinson's Disease Sleep Scale; PIGD, Postural Instability Gait Difficulty; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; VAFS, Visual Analog Fatigue Scale; VAS-Pain, Visual Analog Scale-Pain.

Table 4
Health-related and global quality of life in PD patients with different stage according to the MNCD classification (N = 439)

	Stage 1 (N = 37)	Stage 2 (N = 272)	Stage 3 (N = 124)	Stage 4-5 (N = 6)	p_a	p_b	p_c	p_d
HEALTH-RELATED QOL								
PDQ-39SI	6.65 ± 4.27	15.5 ± 11.24	23.8 ± 16.14	46.36 ± 11.67	<0.0001	<0.0001	<0.0001	0.002
- Mobility	3.91 ± 6.33	12.97 ± 14.67	27.98 ± 24.32	70.83 ± 14.8	<0.0001	<0.0001	<0.0001	0.001
- Activities of daily living	8.77 ± 10.04	17.33 ± 18.25	22.79 ± 21.15	49.97 ± 29.11	<0.0001	0.006	0.018	0.016
- Emotional well-being	9.1 ± 10.13	20.99 ± 20.04	28.6 ± 23.94	38.15 ± 19.23	<0.0001	<0.0001	0.007	0.290
- Stigmatization	7.59 ± 12.67	12.42 ± 18.25	15.16 ± 22.36	20.8 ± 26.39	0.545	0.283	0.842	0.390
- Social support	2.47 ± 9.18	7.19 ± 15.24	11.28 ± 19.7	1.38 ± 3.4	0.014	0.027	0.061	0.252
- Cognition	7.92 ± 9.6	16.94 ± 16.18	27.85 ± 19.95	43.71 ± 14.26	<0.0001	0.001	<0.0001	0.033
- Communication	2.92 ± 6.85	8.26 ± 13.26	12.69 ± 17.52	38.86 ± 24,51	<0.0001	0.011	0.051	0.007
- Pain and discomfort	11.47 ± 13.2	26.93 ± 22.09	32.09 ± 25.68	63.86 ± 16.36	<0.0001	<0.0001	0.112	0.005
GLOBAL QOL								
PQ-10	8 ± 1.38	7.41 ± 1.42	6.65 ± 1.8	5.17 ± 2.78	<0.0001	0.015	<0.0001	0.161
EUROHIS-QOL8	4.18 ± 0.39	3.83 ± 0.52	3.54 ± 0.58	3.12 ± 0.5	<0.0001	<0.0001	<0.0001	0.068
- Quality of life	4.22 ± 0.58	3.87 ± 0.68	3.48 ± 0.75	3.17 ± 0.98	<0.0001	0.004	0.026	0.476
- Health status	3.46 ± 0.86	3.14 ± 0.89	2.91 ± 0.95	2.33 ± 0.81	0.001	0.022	<0.0001	0.148
- Energy	4.3 ± 0.7	3.81 ± 0.78	3.42 ± 0.88	2.83 ± 0.75	<0.0001	<0.0001	<0.0001	0.072
- Autonomy for ADL	4.22 ± 0.67	3.69 ± 0.83	3.23 ± 0.91	2.17 ± 0.41	<0.0001	<0.0001	<0.0001	0.004
- Self-esteem	4.16 ± 0.64	3.87 ± 0.77	3.55 ± 0.91	3.33 ± 0.81	<0.0001	0.035	0.001	0.501
- Social relationships	4.32 ± 0.58	4.12 ± 0.67	3.92 ± 0.73	3.33 ± 0.81	0.001	0.092	0.013	0.064
- Economic capacity	4.3 ± 0.7	3.89 ± 0.77	3.62 ± 0.83	3.83 ± 0.75	<0.0001	0.001	0.002	0.642
- Habitat	4.49 ± 0.51	4.28 ± 0.71	4.23 ± 0.63	4 ± 0	0.149	0.137	0.296	0.245

The results represent mean ± SD. ANOVA and/or Kruskal-Wallis and Mann-Whitney-Wilcoxon test were applied; p_a, all groups; p_b, stage 1 vs. stage 2; p_c, stage 2 vs. stage 3; p_d, stage 3 vs. stage 4. ADL, Activities of daily living; QoL, quality of life.

DISCUSSION

The present study applies the MNCD classification, a novel recently published classification for PD proposed by a Spanish group of experts on PD [4], for the first time in a cohort of PD patients. Interestingly, this transversal analysis observes that different stages for PD proposed in this novel classification correlated very clearly with disease severity and QoL. Moreover, a greater burden in symptoms defined in the MNCD classification (i.e., a higher MNCD total score), with 4 principal axes—Motor, Non-Motor, Cognition, Dependency, correlated with a poorer health-related and global QoL as well.

PD is an incredibly complex illness in which patients can suffer from a wide variety of motor and non-motor symptoms, which cause a progressive worsening in the long-term in QoL and loss of autonomy for ADL [12–14]. Furthermore, PD is very heterogeneous, with different subtypes described related to a variety of etiopathogenic mechanisms involved [15–17], which can explain the differences in the clinical presentation (motor and NMS) of the disease between patients even during the first years of disease duration [18–20]. In this context and taking into account that none of the previous classifications of PD encompasses the disease as a whole [21–24], the MNCD classification was proposed [4] with the idea of being a simple tool to identify key symptoms in PD and monitor the progression of the disease. The TNM classification [25], used in Oncology, was selected as a model and 4 major axes and 5 stages were considered in the design [4]. The four axes were key aspects in PD: Motor Symptoms; Non-Motor symptoms; Cognition; Dependency. Moreover, cognitive impairment and loss of autonomy for ADL were the key factors to define stages 4 and 5 of the MNCD classification. Data obtained from the application of this classification for the first time in a cohort of PD patients agree with great known variability in PD, even in a cohort in which 90% of the patients had a H&Y 1 or 2. The MNCD stage 2 was the most frequent (62%) but up to 28% of the patients had no clinically relevant motor and/or NMS (stage 1). On the contrary, close to 10% of the patients had cognitive impairment and/or dependency for ADL (stage from 3 to 5). Importantly, in many aspects of the disease such as disease duration, LEDD, motor symptoms, NMS, QoL, and autonomy for ADL, a relationship between the stage and the level of affectation was observed, with data indicating a progressive worsening related to disease progression throughout the proposed stages. It would be of great interest applying the MNCD classification in

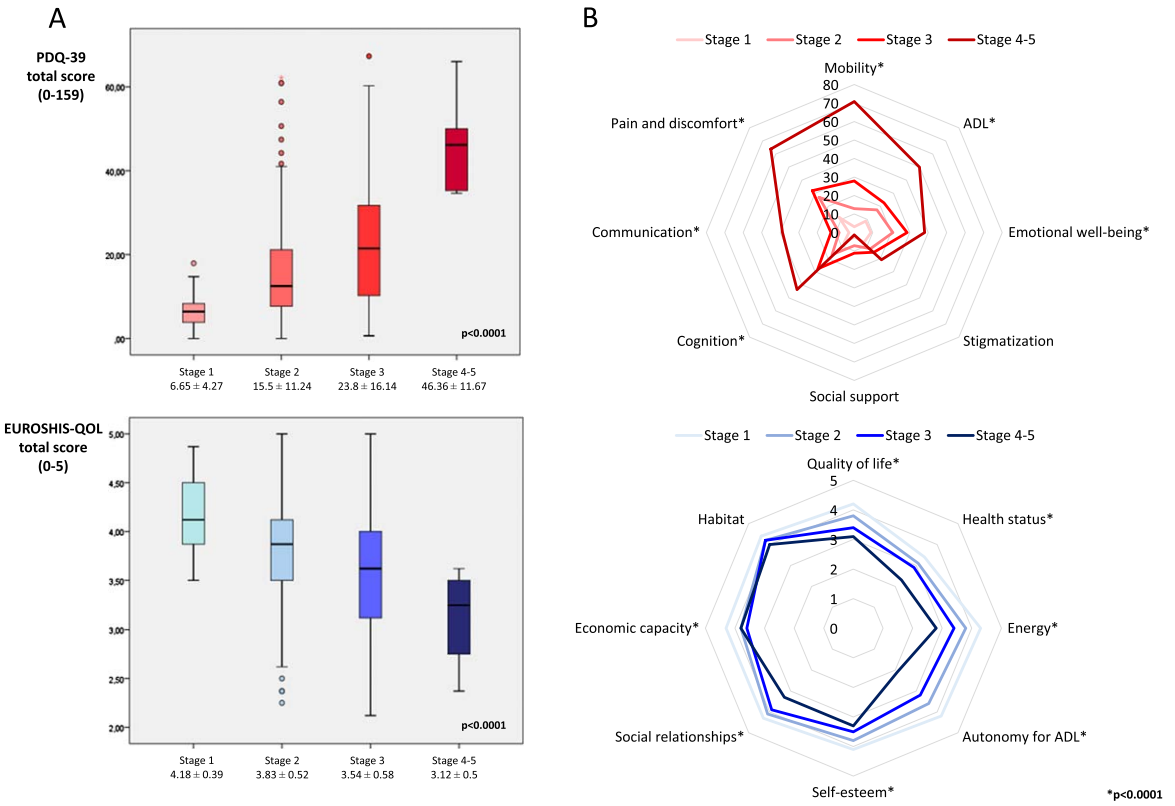

Fig. 2. A) Health-related (PDQ-39SI) and global quality of life (PQ-10 and EUROHIS-QOL8) are represented in patients regarding to the MNCD stage, from stage 0 to stage 4-5. B) Comparison of the mean score on each domain of the PDQ-39SI and EUROHIS-QOL8 between patients regarding the MNCD stage (from 0 to 4-5). *$p < 0.005$. ADL, activities of daily living; EUROHIS-QOL8, EUROHIS-QOL 8-item index; PDQ-39SI; 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index.

a longitudinal analysis with the aim to know if this tool could be useful to monitor the progression of PD, from the first moment (i.e., at diagnosis) to the end (i.e., at death). An adequate classification to use in a neurodegenerative disease such as PD should include symptoms, signs, or biomarkers that are key in decision-making for disease management [26]. Another important point is the high frequency of relevant symptoms and/or complications, such as motor fluctuations (33%), axial symptoms (18%) and especially NMS, with up to 89% of the patients suffering from at least 1 NMS. This aligns with data recently published about the COPPADIS cohort, demonstrating that NMS are very frequent even in patients with a stage 1 or 2 of H&Y, and their identification is very important because NMS impact the patient's QoL independently of the motor stage [27]. Other studies have also observed a high frequency of motor fluctuations and NMS even in early PD patients and demonstrated the relationship between the two [28–33]. From a practical point of view, compared to the H&Y stage, the MNCD classification is also simple but provides much more information including key aspects such as cognitive status and dependency. Moreover, data of this analysis about motor severity assessed with the UPDRS-III and H&Y suggest that the MNCD stages could be useful to monitor changes in motor status along the time.

The principal objective of this study was to compare the QoL between different groups of PD patients from the COPPADIS cohort according to the MNCD stage. The results confirmed our hypothesis, with a very clear significant correlation between the stage and the QoL. The best perceived QoL corresponded to patients in stage 1 and a progressively worse QoL was observed at a more advanced stage of the disease, with stage 4-5 patients having the worst QoL. These results were found both when using the PDQ-39 to assess the health-related QoL and the PQ-10 and the EUROHIS-QOL8 to assess the global QoL.

Moreover, significant differences were detected for all domains of the PDQ-39 (apart from except stigmatization and social support) and EUROHIS-QOL8 (apart from habitat). The strong correlation detected between the burden of symptoms defined in the MNCD classification (MNCD total score, from 0 to 12) and the QoL suggests that this scale could not only be useful for measuring disease progression but also as an indicator of the patient's QoL. In a disease like PD for which there is no cure, improving QoL or at least slowing down its worsening is pivotal and is clearly related to the evolutionary stage [3, 34, 35], which is what the classification aims to measure.

This study has very important limitations. First, the MNCD classification was applied retrospectively using the data previously collected from the COPPADIS cohort PD patients at baseline visit. However, although it was not directly applied by the neurologist during a face-to-face assessment, the criteria for trying to define what symptoms could be considered as clinically relevant symptoms (e.g., major depression, ICD, etc.) were clearly defined for each symptom (Table 1). Second, there is a bias toward less advanced PD in this cohort and the COPPADIS cohort is not fully representative of PD due to inclusion/exclusion criteria at baseline. In fact, only 6 patients were classified as stage 4-5. Specifically and very important in relation with the application of the MNCD classification, patients at baseline with a MMSE <26 and dementia criteria were excluded, explaining why only 1 patient was in stage 5. Moreover, results about the comparison between patients with stage 3 (N = 124) and 4-5 (N = 6) were limited by the sample size. Third, the MNCD classification was applied through a cross-sectional analysis. Although the results are interesting and suggest that the MNCD classification may be useful for monitoring the progression of the disease in PD patients, it is important to be very cautious and the ideal propose would be to apply the MNCD classification in a cohort of early PD patients and follow up to observe the long-term change in the stage as the disease progresses. As an alternative, a cross-sectional analysis in a very large population including advanced or very advanced PD patients would be interesting as well. Even the MNCD classification could be an option to include in PD disease modifying treatment trials or in longitudinal prospective cohort studies [36]. Fourth, as it has been previously commented, the MNCD classification is a proof of concept purpose and a study to analyze the usability and variability of this tool in PD patients is on-going. In this sense, once again, we must still be very cautious when drawing clear conclusions about the classification, since it is necessary to verify beforehand that when it is applied in clinical practice at the discretion of the neurologist, this classification is useful and measures well what it intends. Fifth, a specific scale for the assessment of autonomic symptoms (e.g., SCOPA, etc.) has not been used in the COPPADIS cohort, unlike other cohorts [37], these symptoms may have been underrecognized. In contrast, strengths of our study are the large sample size as a whole (N = 439) and the extensive clinical and demographic information recorded. The results of this study are novel, as this analysis the first time that MNCD classification has been applied in a PD cohort.

In conclusion, we applied the MNCD classification in a PD cohort and observed that staging PD, according to this classification, correlates with QoL and disease severity. The MNCD could be a handy tool to monitor the progression of PD. However, firstly, a validation of the classification, and secondly, more studies designed to apply the MNCD classification in PD patients are needed.

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See the Supplementary Material for the full list of COPPADIS investigators.

CONFLICT OF INTEREST

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McAfee D: None.

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SUPPLEMENTARY MATERIAL

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APPENDIX 1. COPPADIS STUDY GROUP.

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García Moreno, Jose Manuel	Hospital Universitario Virgen Macarena, Sevilla, Spain	Site investigator / PI (until MAR/21)	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
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) - Instituí Cátala de la Salud. 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

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Name (Last Name, First Name)	Location	Role	Contribution
González Ardura, Jessica	Hospital Universitario Lucus Augusti (HULA), Lugo, Spain	Site investigator / PI (until FEB/21)	Evaluation of participants and/or data management
González García, Beatriz	Hospital La Princesa, Madrid, Spain	Site investigator	Nurse study coordinator
González Palmás, Maria 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 Moisés 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
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 (until MAY/22)	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
Lastres Gómez, Sonia	Complejo Hospitalario Universitario de Pontevedra (CHOP), Pontevedra, Spain	Site investigator	Neuropsychologist; evaluation of participants
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

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Name (Last Name, First Name)	Location	Role	Contribution
López Domínguez, Daniel	Institut d'Assistència Sanitària (IAS) - Instituí Cátala de la Salud. Girona, 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
Meitín, Maria 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
Mendoza Plasencia, Zebenzui	Hospital Universitario de Canarias, San Cristóbal de la Laguna, Santa Cruz de Tenerife, 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, Maria 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

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Name (Last Name, First Name)	Location	Role	Contribution
Pagonabarraga, Javier	Hospital de Sant Pau, Barcelona, Spain	Site investigator	Evaluation of participants and/or data management
Pareés, Isabel	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 Moisés 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 (until DEC/19)	Evaluation of participants and/or data management
Prats, Marian Ángeles	Institut d'Assistència Sanitària (IAS) - Instituí Cátala de la Salud. 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
Puig Daví, Arnau	Hospital de Sant Pau, Barcelona, Spain	Site einvestigator	Evaluation of participants and/or data management
Redondo, Nuria	Hospital La Princesa, Madrid, Spain	Site Investigator	Evaluation of participants and/or data management
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

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Name (Last Name, First Name)	Location	Role	Contribution
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) - Instituí Cátala de la Salud. 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