**Benign versus Malignant Parkinson Disease: The Unexpected Silver Lining of Motor Complications**

Aristide Merola, MD, PhD1\*; Alberto Romagnolo, MD2\*; Alok K. Dwivedi, PhD3; Alessandro Padovani, MD, PhD4; Daniela Berg, MD5, 6; Pedro J. Garcia-Ruiz, MD, PhD7; Margherita Fabbri MD, PhD2, 8; Carlo Alberto Artusi, MD2; Maurizio Zibetti, MD, PhD2; Leonardo Lopiano MD, PhD2; Andrea Pilotto, MD4, 9; Sonia Bonacina, MD4; Francesca Morgante, MD, PhD10, 11; Kirsten Zeuner, MD5; Christopher Griewing, MD5; Eva Schaeffer, MD5; Federico Rodriguez-Porcel, MD12; Marcelo Kauffman, MD, PhD13; Pierpaolo Turcano, MD14; Lais M. de Oliveira, MD15; Giovanni Palermo, MD16; Emily Shanks17; Francesca Del Sorbo, MD, PhD18; Salvatore Bonvegna, MD19; Rodolfo Savica, MD, PhD14; Renato P. Munhoz, MD, PhD20; Roberto Ceravolo, MD16; Roberto Cilia, MD19^; Alberto J. Espay, MD, MSc17^

1 Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

2 Department of Neuroscience “Rita Levi Montalcini”, University of Turin, Turin, Italy

3 Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA

4 Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

5 Department of Neurology, Christian-Albrecht-University Kiel, Kiel, Germany

6 Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

7 Department of Neurology, Movement Disorders Unit, Fundacion Jimenez Diaz, Universidad Autonoma de Madrid, Madrid, Spain

8 Laboratory of Pharmacology and Therapeutics, Facultade de Medicina, Universidade de Lisboa, Lisbon, Portugal

9 Parkinson’s Disease Rehabilitation Centre, FERB ONLUS – S. Isidoro Hospital, Trescore Balneario (BG), Italy

10 Neurosciences Research Centre, Molecular and Clinical Sciences Institute, St George's University of London, London, UK

11 Dipartimento di Medicina Clinica e Sperimentale, Università di Messina, Messina, Italy

12 Department of Neurology, Medical University of South Carolina, Charleston, SC, USA

13 Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurologia "José María Ramos Mejía" y Division Neurologia, Hospital J.M.Ramos Mejia, Facultad de Medicina, UBA, Buenos Aires, Argentina

14 Department of Neurology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, USA

15 Edmond J. Safra Program in Parkinson’s Disease, Morton and Gloria Shulman Movement Disorders Clinic, University Health Network, Toronto Western Hospital, Division of Neurology, University of Toronto, Toronto, Ontario, Canada

16 Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

17 Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

18 Parkinson Institute, ASST Gaetano Pini-CTO, Milan, Italy

19 Fondazione IRCCS Istituto Neurologico Carlo Besta, Movement Disorders Unit, Milan, Italy

20 Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Krembil Brain Institute, Toronto, Ontario, Canada

\*: these authors contributed equally and shared co-first authorship

^: these authors contributed equally and shared co-senior authorship

**Corresponding Author:** Aristide Merola, MD, PhD

Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Tel: +1(513)-362-9165

e-mail: Aristide.Merola@osumc.edu

**Word Count:** 3132

**ABSTRACT**

**Objective:** We sought to evaluate demographic, clinical, and habits/occupational variables between phenotypic extremes in Parkinson’s disease (PD).

**Methods:** Databases from 9 movement disorders centers across 7 countries were retrospectively searched for subjects meeting criteria for very slowly progressive, benign, PD (bPD) and rapidly progressive, malignant, PD (mPD). bPD was defined as Hoehn and Yahr (H&Y) stage ≤3, normal cognitive function, and Schwab and England (S&E) score ≥70 after ≥20 years of PD (≥10 years if older than 60 at PD onset); mPD as H&Y >3, S&E score <70, and cognitive impairment within 10 years from PD onset. We performed between-group analysis of demographic, habits/occupational, and clinical features at baseline and follow-up and unsupervised data-driven analysis of the clinical homogeneity of bPD and mPD.

**Results:** At onset, bPD subjects (n=210) were younger, had a single limb affected, lower severity and greater asymmetry of symptoms, and lower prevalence of depression than mPD (n=155). bPD was associated with active smoking and physical activity, mPD with agricultural occupation. At follow-up, mPD showed higher prevalence of depression, hallucinations, dysautonomia, and REM behaviour disorder. Interestingly, the odds of mPD were significantly reduced by the presence of dyskinesia and wearing-off. Data-driven analysis confirmed the independent clustering of bPD and mPD, with age at onset emerging as a critical discriminant between the two groups (<46-year-old vs. >68-year-old).

**Conclusions:** Phenotypic PD extremes showed distinct demographic, clinical, and habits/occupational factors. Motor complications may be conceived as markers of therapeutic success given their attenuating effects on the odds of mPD.

**Keywords:** Parkinson, Epidemiology, Benign, Malignant, Aging, Motor Complications.

**DECLARATIONS**

**Funding sources**

Nothing to declare

**Financial disclosure related to research covered in this article**

None

**Financial disclosures and Conflicts of interest**

Dr Merola is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL Behring, Abbvie, and Cynapsus Therapeutics. He has received grant support from Lundbeck.

Dr Romagnolo has received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco, Chiesi Farmaceutici, Medtronic, and UCB Pharma.

Dr. Dwivedi is supported as a co-investigator by the NIH (1R01HL125016-01), (1 R21 HL143030-01) and (1R21 AI133207) grants and as a collaborator in NIH R21 AI118228 grant. He has been also serving as a statistician in CPRIT grants (PP180003, PP170068, PP170004, PP140164, 140211, PP110156, PP150031, and PP130083), CCTST K12 (consultant) award, Coldwell (co-investigator) and TMF (co-investigator).  Dr. Dwivedi is a director of Biostatistics & Epidemiology Consulting Lab at the TTUHSC EP.

Dr. Padovani has received grant support from Ministry of Health (MINSAL) and Ministry of Education, Research and University (MIUR), from CARIPLO Foundation; personal compensation as a consultant/scientific advisory board member for Avanir, Lundbeck, Eli-Lilly, Neuraxpharma, Biogen, GE Health.

Dr. Berg reports grants from Janssen Pharmaceutica, grants from Damp foundation, grants from German Parkinson’s Disease Association (dPV), grants from BMWi, grants from BMBF, grants from Parkinson Fonds Deutschland GmbH, grants and speaker’s honoraria from and consultancies for UCB Pharma GmbH, grants from Novartis Pharma GmbH, grants and speaker’s honoraria from and consultancies for Lundbeck, speaker’s honoraria from and consultancies for BIAL, grants from the EU, speaker’s honoraria from and consultancies for Biogen, and speaker’s honoraria from AbbVie, Zambon and Desitin.

Dr. Garcia-Ruiz has received research support from Allergan and UCB, personal compensation as a consultant/scientific advisory board from Italfarmaco, Britannia, Bial, Zambon, and speaker’s honoraria from Italfarmaco, UCB, Zambon, Allergan and Abbvie.

Dr. Fabbri has no financial conflicts to disclose.

Dr. Artusi has received travel grants from Zambon and Abbvie.

Dr. Zibetti has received honoraria from Medtronic, Zambon Pharma and AbbVie

Dr. Lopiano has received honoraria for lecturing and travel grants from Medtronic, UCB Pharma, and AbbVie.

Dr. Pilotto has received speaker honoraria from BioMarin Pharmaceutical, Chiesi Pharmaceuticals, Nutricia Pharmaceuticals, UCB Pharma and Zambon Pharmaceuticals. He received grants from the Italian Ministry of Health, Zambon Italia, Vitaflo Germany.

Dr. Bonacina has no financial conflicts to disclose.

Dr. Morgante has received speaking honoraria from Medtronic, Zambon, Chiesi, Abbvie, Merz, Bial; personal compensation as a consultant/scientific advisory board member from Merz, Abbvie, Bial, Medtronic

Dr. Zeuner has received research support from an intramural grant from the Christian-Albrechts-University of Kiel, from the Benign Essential Blepharospasm Research Foundation and with an unrestricted grant from Ipsen. She has received lecture fees from Allergan, Merz, AbbVie and Bayer outside the submitted work. She has served as a consultant and received fees from Merz and Ipsen.

Dr. Griewin has no financial conflicts to disclose.

Dr. Schaeffer has received intramural research funding from the University of Kiel and speaker’s honoraria from Bayer Vital GmbH and Novartis.

Dr. Rodriguez-Porcel has no financial conflicts to disclose.

Dr. Kauffman is an employee of the CONICET. He has received grant support from Ministry of Science and Technology of Argentina and Ministry of Health of Buenos Aires. He has received honoraria payments for educational activities from Janssen Pharmaceuticals and Bago Pharmaceuticals.

Dr. Turcano has no financial conflicts to disclose

Dr. de Oliveira has no financial conflicts to disclose.

Dr. Palermo has no financial conflicts to disclose

Ms. Shanks has no financial conflicts to disclose.

Dr. Del Sorbo has no financial conflicts to disclose.

Dr. Bonvegna has no financial conflicts to disclose.

Dr. Savica has received research support from the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, the Mayo Clinic Small Grants Program National Center for Advancing Translational Sciences (NCATS), and unrestricted grant from ACADIA Pharmaceuticals, INC.

Dr. Munhoz has no financial conflicts to disclose.

Dr. Ceravolo has received fees for speech by Abbvie, General Electric, Zambon, UCB, Lusofarmaco.

Dr. Cilia has has received speaking honoraria from Zambon, UCB, Bial; personal compensation as a consultant from Roche.

Dr. Espay has received grant support from the NIH, Great Lakes Neurotechnologies and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, TEVA, Impax, Acadia, Acorda, Intrance, Cynapsus/Sunovion, Lundbeck, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from Abbvie, UCB, USWorldMeds, Lundbeck, Acadia, the American Academy of Neurology, and the [Movement Disorders](https://www.sciencedirect.com/topics/medicine-and-dentistry/movement-disorders) Society.

**Ethics approval**

The study received IRB/ethics committee approval at all participating centers and was conducted in accordance with the Good Clinical Practice and the International Conference on Harmonization guidelines and any applicable national and local regulations.

The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Data access and responsibility statement**

A. Merola had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Authorship statement**

Aristide Merola: study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content.

Alberto Romagnolo: study concept and design, acquisition and interpretation of data, drafting/revising the manuscript for content.

Alok K. Dwivedi: analysis and interpretation of data, drafting/revising the manuscript for content.

Alessandro Padovani: interpretation of data, revising the manuscript for content.

Daniela Berg: interpretation of data, revising the manuscript for content.

Pedro J. Garcia-Ruiz: acquisition of data, revising the manuscript for content.

Margherita Fabbri: acquisition of data, revising the manuscript for content.

Carlo Alberto Artusi: acquisition of data, revising the manuscript for content.

Maurizio Zibetti: acquisition of data, revising the manuscript for content.

Leonardo Lopiano: interpretation of data, revising the manuscript for content.

Andrea Pilotto: acquisition of data, revising the manuscript for content.

Sonia Bonacina: acquisition of data, revising the manuscript for content.

Francesca Morgante: interpretation of data, revising the manuscript for content.

Kirsten Zeuner: acquisition of data, revising the manuscript for content.

Christopher Griewing: acquisition of data, revising the manuscript for content.

Eva Schaeffer: interpretation of data, revising the manuscript for content.

Federico Rodriguez-Porcel: acquisition of data, revising the manuscript for content.

Marcelo Kauffman: interpretation of data, revising the manuscript for content.

Pierpaolo Turcano: acquisition of data, revising the manuscript for content.

Lais M. de Oliveira: acquisition of data, revising the manuscript for content.

Giovanni Palermo: acquisition of data, revising the manuscript for content.

Emily Shanks: acquisition of data, revising the manuscript for content.

Francesca Del Sorbo: acquisition of data, revising the manuscript for content.

Salvatore Bonvegna: acquisition of data, revising the manuscript for content.

Rodolfo Savica: interpretation of data, revising the manuscript for content.

Renato P. Munhoz: interpretation of data, revising the manuscript for content.

Roberto Ceravolo: interpretation of data, revising the manuscript for content.

Roberto Cilia: study concept and design, interpretation of data, revising the manuscript for content.

Alberto Espay: study concept and design, interpretation of data, revising the manuscript for content.

All the co-authors listed above gave their final approval of this manuscript version.

All the co-authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Acknowledgments**

Authors acknowledge the contribution of the “Fondazione Grigioni per il Morbo di Parkinson”, Milan, Italy

**INTRODUCTION**

Despite a consensus on the unifying pathological hallmark, α-synuclein-filled Lewy bodies and Lewy neurites, the clinical, pathological, and biological boundaries of Parkinson disease (PD) remain poorly defined [1]. At a clinical level, most patients with PD will eventually develop motor and non-motor disability milestones and levodopa-resistant symptoms such as dementia, dysphagia, postural instability, and falls [2], with a median survival time from motor onset of 15.8 years [3]. However, PD progression is heterogeneous [4-7]. On the malignant end, the phenotype includes rapidly progressive marked axial symptoms and cognitive impairment within 10 years from symptom onset (mPD); on the benign end, mild to moderate, very slowly progressive disability, with no dementia accruing after more than 20 years of disease (bPD) [8, 9]. The factors that lead to this variability remain undetermined.

Prior studies have identified a growing list of proposed multidimensional data-driven PD subtypes [10-12]. However, these subtypes lacked reproducibility in a well-characterized cohort of patients [13] and proved to be inadequate to predict postmortem severity or distribution of pathological findings [14]. Still, certain clinical phenotypes (e.g., young age at onset, tremor-dominant) are known to be associated with a benign PD subtype, while others (e.g., orthostatic hypotension, REM sleep behavior disorder (RBD), non-tremor dominant) correlate with early functional decline and reduced life-expectancy [6, 15, 16]. Lastly, epidemiological studies have demonstrated a complex interaction between PD and exposure to environmental factors such as pesticides, metals, or other toxins, emphasizing the importance of multiple environmental factors (exposome) in the cascade of pathological processes associated with neurodegenerative disorders[17].

We hypothesized that the phenotypic extremes bPD and mPD are associated with other demographic, clinical, response to therapy, and life habits/occupational variables beyond their slower and more rapid progression, respectively.

**METHODS**

**Definitions and Eligibility Criteria**

Through the consensus of 9 specialized movement disorders centers from 7 countries (United States, Italy, Spain, Argentina, Germany, United Kingdom, and Canada), we designed a retrospective cohort study of idiopathic PD patients meeting UK PD Brain Bank definition [18] and the following criteria for bPD and mPD: (1) bPD was defined by the combination of a Hoehn and Yahr (H&Y) stage ≤ 3 (daily medication-ON condition), preserved cognitive function, defined as a Montreal Cognitive Assessment ≥ 26 or Mini Mental Status Examination Scale ≥ 24 [19, 20], and independence in activities of daily living (ADL) documented by a score ≥ 70 on the Schwab and England scale [21] after ≥ 20 years from symptom onset (or ≥ 10 years in patients with age at PD onset > 60 years-old). (2) mPD was defined as the combination of H&Y stage > 3 (daily medication-ON condition), significant ADL impairment documented by a score < 70 at the Schwab and England [21], and cognitive impairment or dementia (Montreal Cognitive Assessment < 26 and/or Mini Mental Status Examination Scale < 24 [19, 20]) appearing within 10 years from symptom onset. We excluded patients with atypical features suggestive of an alternative form of parkinsonism, antidopaminergic drug exposure, and dementia and/or hallucinations within 12 months from symptom onset.

**Data Collection**

Between November 2018 and May 2019, patients were screened during their scheduled follow-up visit in each of the centers involved. Then, medical records were reviewed for demographic information on gender, age, age at onset, ethnical background, working activity (Dictionary of Occupational Titles (DOT) codes [22]), and family history of movement disorders, as well as the following clinical data collected during the first neurological evaluation within 5 years from symptom onset (baseline visit), and at the last follow-up available:

*Motor symptoms*. Disease duration, handedness, body side and segment (upper vs. lower limbs) affected at onset, Unified PD Rating Scale (UPDRS) part III [23] score in the ON medication state, H&Y stage in the ON state, Schwab and England score in the ON state. Also, clinical charts and UPDRS parts II, III, and IV scores were reviewed for presence and severity of wearing-off, freezing of gait, dyskinesia, and postural abnormalities including camptocormia and Pisa syndrome.

*Non-Motor Symptoms*. Depression, hallucinations, autonomic dysfunction, including orthostatic hypotension, drooling, bladder dysfunction, and sexual dysfunction (data retrieved from the reviews of systems available on clinical notes); and RBD, diagnosed according to the “single question screen” [24].

*Therapeutic regimen*. The total levodopa equivalent daily dose (LEDD) was calculated according to a validated conversion table [25] including the daily dose of levodopa (immediate release and extended release formulations), dopamine agonists, monoaminoxidase-B inhibitors (iMAO-B), catechol-O-methyltransferase inhibitors (i-COMT), and amantadine.

We included in the analyses age-related comorbidities (hypertension, myocardial infarction, peripheral arterial disease, diabetes, stroke, vascular encephalopathy, hypercholesterolemia).

The annual progression rate was computed using the following formula: (UPDRS-III at the last follow-up – UPDRS-III at baseline) / (age at last follow-up – age at baseline). In addition, data on smoking and alcohol intake and physical activity, defined as a minimum of 30 minutes five days/week and/or 20 minutes of vigorous physical activity on at least three days/week [26] were obtained at the baseline evaluation. Missing data or discordant information were acquired/clarified with a telephone or in-person clinical interview.

Standardized form of data collection and instruments were used to minimize biases in data recording and interpretation. Patients with incomplete records, or for whom a precise collection of data was not possible were excluded from the study. A third reviewer verified the random data to ensure the validity of different diagnosis or symptom characteristics across different countries/practices.

**Data Analysis**

Comparisons of baseline characteristics between bPD and mPD groups were carried out using Chi square/Fisher’s exact test for categorical variables and unpaired t-test for quantitative variables. All the significant characteristics were compared according to each age group at onset compared to the rest of age-groups using Fisher’s exact test. A multivariable logistic regression analysis was used to determine adjusted associations of cofactors with mPD compared to bPD. The backward stepwise procedure with the probability of removal at 15% was applied for selecting appropriate factors in multivariable analysis. The results of logistic regression analysis were summarized using the odds ratio (OR), 95% confidence interval (CI), and p-value. Further, the results of the logistic regression model were validated after imputing missing data using multiple imputation (MI) method. In the imputation analysis, 10 datasets were imputed. Each dataset was analyzed using logistic regression analyses, and results from each model were pooled to obtain model estimates. Separate adjusted analyses were carried out for differentiating mPD from bPD using baseline and follow up variables. The association of covariates with the rate of UPDRS III score progression was determined using linear regression analysis and results were presented with regression coefficients (RC) and p-values.

A latent profile analysis (LPA) was used to determine the number of latent groups which can differentiate unknown slow or rapidly progressive PD groups irrespective of the *a priori* definition of bPD and mPD, based on demographic and clinical characteristics of patients. The number of clustering was determined using Voung-Lo-Mendell-Rubin likelihood ratio test (LRT) and adjusted LRTs. A significant p-value of LRTs indicates the best fit for a model with k-classes compared to a model with k-1 classes. The posterior class probabilities from the developed model were used to classify individuals in different latent classes and compared with the previously obtained PD groups. The LPA results were further validated after multiple imputations for missing data with 10 datasets as described above.

P-values less than or equal to 5% were considered statistically significant. All analyses were conducted using STATA 15 while the LPA was conducted using MPLUS 7.4.

**Sample Size Considerations and Handling of Missing Data**

We used published data for the sample size calculation. Although with methodological differences, Fereshtehnejad et al. [10]demonstrated 5 disease characteristics (with moderate effect size, odds ratio varying from 1.41-2.45) associated with rapid PD progression compared to benign/average PD progression with 17% prevalence of benign and rapid PD prevalence. We also expected some disease characteristics moderately associated (OR=1.4) with mPD compared to bPD. Using this information, we estimated that a total sample size of 340 was sufficient to detect significant factors moderately associated with bPD and mPD with 80% power using a logistic regression analysis with 15% variance explained by other factors at 5% level of significance. Further, we estimated that this sample size was sufficient to test 25 predictors assuming 10-15 subjects per predictor [27]. This sample size was also powered (80%) to determine 2-4 latent classes using 9-15 variables with moderate effect size using a latent profile analysis [28]. Data with > 30% of missing values were excluded from the analyses.

**Ethics**

The study received IRB/ethics committee approval at all participating centers and was conducted in accordance with the Good Clinical Practice and the International Conference on Harmonization guidelines and any applicable national and local regulations. All General Data Protection Regulation requirements for data collection were met.

**RESULTS**

**Patients**

Screening of available databases resulted in the identification of 428 patients meeting criteria for bPD (n= 264) or mPD (n= 164): 365 (210 bPD and 155 mPD) were included in the analysis and 63 excluded due to incomplete clinical data (Online Resource 1).

*Demographics*. The two groups were comparable in sex, ethnicity, handedness, and family history of neurological disorders (Table 1). Age at onset differed between groups (Figure 1): 60% bPD vs. 1.9% mPD had an onset under 50 years (p< 0.001); 26.2% bPD vs. 12.3% mPD between 51 and 60 years (p= 0.001); 11.9% bPD vs. 38.1% mPD between 61 and 70 years (p< 0.001); and 1.9% bPD vs. 47.7% mPD after 70 years (p< 0.001).

**Baseline**

At disease onset, bPD was associated with higher asymmetry of symptoms (p< 0.001), greater prevalence of single limb (arm or leg) involvement (p< 0.001), lower UPDRS-III scores (p< 0.001), and lower prevalence of depression (p< 0.001) (Table 1).

There was a significant difference in occupational exposure and habits between the two groups: mPD was associated with higher prevalence of agricultural occupations (p< 0.05; Table 1), bPD with higher prevalence of active smokers (p= 0.046) and with regular physical activity (p< 0.001; Figure 2). In multivariable analysis, mPD was associated with older age at onset (OR: 1.326; 95%CI: 1.196-1.470; p< 0.001); involvement of both upper and lower limbs (OR: 11.059; 95%CI: 2.079-58.819; p= 0.005); lack of physical activity (OR: 8.621; 95%CI: 1.140-66.667; p= 0.037); depression (OR: 6.140; 95%CI: 1.567-24.061; p= 0.009); and higher UPDRS-III score (OR: 1.228; 95%CI: 1.125-1.340; p< 0.001). In validation analyses after imputing missing data, older age at onset, lack of physical activity, depression, and higher UPDRS-III remained significant (Online Resource 1).

**Follow-up**

By design, at the last follow up there were significant differences in disease duration: bPD patients had accrued a mean disease duration of 20.8 ± 4.2 years, whereas mPD patients of 9.2 ± 3.2 years (p<0.001). Validating the separation between groups, the annual rate of UPDRS-III progression differed between the groups, slower in bPD and faster in mPD (p< 0.001).

bPD was associated with greater prevalence of wearing-off (p< 0.001) and dyskinesia (p< 0.001), lower prevalence of freezing of gait (p< 0.001) and postural abnormalities (p< 0.001), and higher dosages of dopaminergic medications (p< 0.001) (Table 2). While none of the mPD patients underwent subthalamic nucleus deep brain stimulation (DBS), 52/210 bPD patients (24.7%) did. Their mean duration of post-surgical follow up was 7.2 ± 3.8 years. There was a similar prevalence of age-related comorbidities in the two groups (45.2% for bPD vs. 47.1% for mPD; p= 0.794).

mPD was associated with a higher proportion of depression (p< 0.001), hallucinations (p< 0.001), autonomic dysfunction (p< 0.001), and RBD (p< 0.001). In multivariable analysis, the odds of mPD increased with freezing of gait (OR: 6.221; 95%CI: 1.621-21.132; p= 0.006), trunk posture alterations (OR: 5.334; 95%CI: 1.901-15.116; p= 0.001), depression (OR: 14.412; 95%CI: 3.259-65.321; p< 0.001), hallucinations (OR: 49.243; 95%CI: 13.312-179.876; p< 0.001) and autonomic dysfunction (OR: 6.034; 95%CI: 1.897-23.545; p= 0.004). These odds were reduced by the presence of dyskinesia (OR: 0.175; 95%CI: 0.048-0.603; p= 0.005) and wearing-off (OR: 0.221; 95%CI: 0.058-0.742; p= 0.015) both before and after adjusting for UPDRS progression. In the validation analysis, after imputing missing data, all variables remained statistically significant except for wearing-off (Online Resource 2).

Motor fluctuations were associated with younger age at PD onset and higher LEDD in both groups and with an asymmetric PD onset in mPD. No associations were observed between gender, UPDRS-III at onset and at follow-up, or UPDRS-III annual progression rate and motor fluctuations (Table 3).

**Clustering based on clinical and demographic characteristics of patients**

The unsupervised data-driven analysis confirmed an independent clustering of bPD and mPD according to baseline clinical characteristics, with age at onset emerging as a critical discriminant between the two groups (< 46-year-old in bPD and > 68-year-old in mPD; Online Resource 2). Patients with age at onset between 60 and 70 years showed partial overlap in baseline clinical features, followed by divergent clinical evolutions over follow-up (Figure 3). bPD was associated with an asymmetric clinical presentation involving the upper or lower limb, UPDRS-III at onset < 10, and physical activity. mPD was associated with a symmetric clinical presentation involving both upper and lower limbs, UPDRS-III at onset > 20, agricultural occupation, and history of depression (Online Resource ~~2~~ 3).

**DISCUSSION**

Several conclusions from this analysis confirmed prior observations regarding the differential features of benign versus malignant ends of the phenotypic spectrum. The benign phenotype of PD was associated with a younger age at onset, asymmetric clinical presentation in one limb, and a greater prevalence of regular physical exercise and active smoking; the malignant phenotype with freezing of gait, postural abnormalities, hallucinations, and autonomic dysfunction, and a greater prevalence of depression and agricultural occupation. The novelty of the analysis is in revealing a “silver lining” to aspects about therapy usually feared: higher dopaminergic dose as well as greater wearing off and dyskinesia were significantly more common in bPD than mPD. In addition, since the presence of motor fluctuations were associated with higher dosage of dopaminergic medications and lower odds of mPD, it is conceivable that a “malignant” course in PD may be contributed to, at least in part, by under-dopaminergic replacement.

The unsupervised data-driven analysis confirmed the validity of the a-priori clustering of bPD and mPD and identified age at onset, along with baseline motor severity, depression, and physical activity as critical distinguishing variables between these divergent clinical phenotypes [14, 29, 30]. bPD patients were more likely to have an onset under the age of 46 years, be engaged in regular physical activity, and present with an asymmetric onset, single limb involvement, and mild severity of motor symptoms. Conversely, mPD patients were more likely to have an onset after the age of 68 years, to have been employed in an agricultural profession, and present with depression, symmetric motor onset, moderate severity of motor symptoms, and involvement of both upper and lower limbs. Interestingly, bPD and mPD patients with age at PD onset in the seventh decade showed overlap in baseline clinical characteristics.

The data highlight the importance of age at onset as a critical factor differentiating the subtypes at the end of the phenotypic PD spectrum, as well as the risk for motor complications. Also, our findings suggest that a combination of modifiable environment and lifestyle factors contribute to their differential expression. Prior epidemiological studies have confirmed the beneficial effects of regular physical exercise [31, 32], although we cannot exclude that those in the mPD group reported lower physical activity at baseline due to their older age at PD onset or other selection biases. On the other end, detrimental effects associated with exposure to pesticide are well documented [33, 34], although ours stand in contrast with a reported association with tremor-dominant PD [35]. This might be partly explained by a recognition bias towards earlier and more accurate diagnosis in patients with tremor-dominant vs. akinetic-rigid PD, particularly in rural contexts with limited access to care.

The possibility exists that age-related compensatory mechanisms might have played a role on the observed results [36-38], but it seems also likely that the two divergent clinical phenotypes of bPD and mPD are manifestations of substantial biological divergence [39]. The bulk of differences between groups likely obey molecular, biological, and neuroanatomical factors. However, the positive association with motor complications, wearing off and dyskinesia, indicates preservation of cortico-striatal dopaminergic connections [40] with changes in synaptic plasticity [41, 42] maybe associated with younger age at PD onset [43]. Such effects are partly dependent on a therapeutic dose of levodopa and argue against aiming at low levodopa replacement [44, 45]. This may not be feasible in a subset of mPD patients in whom higher levodopa doses may induce or worsen hallucinations or autonomic dysfunction and response to treatment may be reduced to more widespread degeneration, well beyond the nigro-striatal system, including cholinergic [46], serotoninergic [47] and noradrenergic involvement [48]. Relatedly, our study confirms the strong association between RBD/OH and early cognitive impairment in mPD [49, 50].

These conclusions are tempered by several limitations. First, these retrospectively collected data may have been affected by recall and selection biases, which we aimed to minimize by involving several tertiary centers experienced in clinical research on PD. Second, the unequal lengths of follow-up duration, expected by virtue of the study design, precludes adjusting for disease duration or other age-dependent variables. Third, a minority of patients underwent the baseline evaluation after almost 5 years since the PD onset, although not surprisingly considering the delay frequently associated with the diagnosis of PD, especially in the akinetic-rigid phenotypes. Fourth, the clinical definition of bPD and mPD, although based on consensus from multiple international experts, are arbitrary. We opted for applying criteria based on the H&Y and MMSE/MoCA due to their wide diffusion and well-defined cut-offs. These criteria were further supported by the Schwab and England score, a validated instrument of daily living functional activities. Fifth, the lack of scales for assessing non-motor symptoms, which have only recently become available [51], were not administered at baseline. Sixth, the large majority of patients in both bPD and mPD group were Caucasian. Although the ethnic background was considered as a biological variable in the analyses, the disproportionate representation of Caucasian patients limits the generalizability of our results. Finally, the lack of genetic, neuroimaging, and pathological data partially limit the generalizability of our findings.

These limitations notwithstanding, our data showed that beyond anticipated differences in age at onset, susceptibility to occupational and lifestyle factors, clinical presentation, and functional systems involved, dyskinesia and wearing off emerged as motor complications of high prevalence in bPD exerting attenuating effects on the odds of mPD. These levodopa-dependent motor complications may be considered important markers of therapeutic success. Although these divergent clinical phenotypes may be mostly impacted by age-related mechanisms, the data suggests that an aggressive dopamine replacement strategy may attenuate the “malignant” end of the spectrum. Future research endeavors will need to examine molecular underpinnings, genetic variables, and gene-environment interactions underpinning the variability in phenotypes.

**REFERENCES**

1. Berg D, Postuma RB, Bloem B et al (2014) Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord 29:454-462

2. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG (2008) The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 23:837-844

3. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G (2010) What predicts mortality in Parkinson disease?: a prospective population-based long-term study. Neurology 75:1270-1276

4. Schrag A, Schott JM (2006) Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol 5:355-363

5. Ahlskog JE (2007) Beating a dead horse: dopamine and Parkinson disease. Neurology 69:1701-1711

6. Kempster PA, O’Sullivan SS, Holton JL, Revesz T, Lees AJ (2010) Relationships between age and late progression of Parkinson’s disease: a clinico-pathological study. Brain 133:1755–1762

7. Coelho M, Ferreira JJ (2012) Late-stage Parkinson disease. Nat Rev Neurol 8:435–442

8. Romagnolo A, Fabbri M, Merola A et al (2018) Beyond 35 years of Parkinson's disease: a comprehensive clinical and instrumental assessment. J Neurol 265:1989-1997

9. Merola A, Zibetti M, Angrisano S et al (2011) Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients. Brain 134:2074-2084

10. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB (2015) New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes. JAMA Neurol 72:863-873

11. Erro R, Vitale C, Amboni M et al (2013) The heterogeneity of early Parkinson’s disease: a cluster analysis on newly diagnosed untreated patients. PLoS One 8:e70244

12. Van Rooden SM, Heiser WJ, Kok JN, Verbaan D, van Hilten JJ, Marinus J (2010) The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. Mov Disord 25:969-978

13. Mestre TA, Eberly S, Tanner C et al (2018) Reproducibility of data-driven Parkinson's disease subtypes for clinical research. Parkinsonism Relat Disord 56:102-106

14. De Pablo-Fernández E, Lees AJ, Holton JL, Warner TT (2019) Prognosis and Neuropathologic Correlation of Clinical Subtypes of Parkinson Disease. JAMA Neurol 76:470-479

15. Pilotto A, Romagnolo A, Tuazon JA et al (2019) Orthostatic hypotension and REM sleep behaviour disorder: impact on clinical outcomes in α-synucleinopathies. J Neurol Neurosurg Psychiatry 90:1257-1263

16. Postuma RB, Bertrand J-A, Montplaisir J et al (2012) Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson’s disease: a prospective study. Mov Disord 27:720-726

17. Tanner CM, Goldman SM, Ross GW, Grate SJ (2014) The disease intersection of susceptibility and exposure: chemical exposures and neurodegenerative disease risk. Alzheimers Dement 10:S213-225

18. Gibb WRG, Lees AJ (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson’s disease. J Neurol Neurosurg Psychiatry 51:745-752

19. Nasreddine ZS, Phillips NA, Bédirian V et al (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695-699

20. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189-198

21. Schwab J, England A (1969) Projection technique for evaluating surgey in Parkinson’s disease. In: Gillingham F, Donaldson M (eds) Third Symposium on Parkinson’s Disease. Churchill Livingstone, Edinburgh, pp 152-157

22. Miller AR, Trieman DJ, Cain PS, Roos PA (1980) Work, jobs, and occupations: a critical review of the dictionary of occupational titles. National Academy Press, Washington

23. Fahn S, Elton RL (1987) UPDRS Development Committee. The Unified Parkinson’s Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M (eds) Recent Developments in Parkinson’s Disease, 2nd edn. Macmillan Health Care Information, Florham Park, pp 153-163

24. Postuma RB, Arnulf I, Hogl B et al (2012) A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study. Mov Disord 27:913-916

25. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25:2649-2653

26. Arias-Palencia NM, Solera-Martínez M, Gracia-Marco L et al (2015) Levels and Patterns of Objectively Assessed Physical Activity and Compliance with Different Public Health Guidelines in University Students. PLoS One 10:e0141977

27. Harris RJ (1985) A primer of multivariate statistics, 2nd edn. Academic Press, New York

28. Dziak JJ, Lanza ST, Tan X (2014) Effect Size, Statistical Power and Sample Size Requirements for the Bootstrap Likelihood Ratio Test in Latent Class Analysis. Struct Equ Modeling 21:534-352

29. Lewis SJ, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA (2005) Heterogeneity of Parkinson’s disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry 76:343-348

30. Ascherio A, Schwarzschild MA (2016) The epidemiology of Parkinson’s disease: risk factors and prevention. Lancet Neurol 15:1257-1272

31. Marras C, Canning CG, Goldman SM (2019) Environment, lifestyle, and Parkinson's disease: Implications for prevention in the next decade. Mov Disord 34:801-811

32. Hirsch MA, Iyer SS, Sanjak M (2016) Exercise-induced neuroplasticity in human Parkinson's disease: What is the evidence telling us? Parkinsonism Relat Disord 22 Suppl 1:S78-81

33. Ahmed H, Abushouk AI, Gabr M, Negida A, Abdel-Daim MM (2017) Parkinson's disease and pesticides: A meta-analysis of disease connection and genetic alterations. Biomed Pharmacother 90:638-649

34. Fitzmaurice AG, Rhodes SL, Cockburn M, Ritz B, Bronstein JM (2014) Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease. Neurology 82:419-426

35. Moisan F, Spinosi J, Delabre L et al (2015) Association of Parkinson's Disease and Its Subtypes with Agricultural Pesticide Exposures in Men: A Case-Control Study in France. Environ Health Perspect 123:1123-1129

36. Calabrese V, Santoro A, Monti D et al (2018) Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. Free Radic Biol Med 115:80-91

37. de la Fuente-Fernández R, Schulzer M, Kuramoto L et al (2011) Age-specific progression of nigrostriatal dysfunction in Parkinson's disease. Ann Neurol 69:803-810

38. Brotchie J, Fitzer-Attas C (2009) Mechanisms compensating for dopamine loss in early Parkinson disease. Neurology 72:S32-38

39. Espay AJ, Lang AE (2018) Parkinson Diseases in the 2020s and Beyond: Replacing Clinico-Pathologic Convergence With Systems Biology Divergence. J Parkinsons Dis 8:S59-64

40. Picconi B, Centonze D, Håkansson K et al (2003) Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. Nat Neurosci 6:501-506

41. Iravani MM, McCreary AC, Jenner P (2012) Striatal plasticity in Parkinson's disease and L-dopa induced dyskinesia. Parkinsonism Relat Disord 18:S123-125

42. Espay AJ, Morgante F, Merola A et al (2018) Levodopa-induced dyskinesia in Parkinson disease: Current and evolving concepts. Ann Neurol 84:797-811

43. Kishore A, James P, Krishnan S, Yahia-Cherif L, Meunier S, Popa T (2017) Motor cortex plasticity can indicate vulnerability to motor fluctuation and high L-DOPA need in drug-naïve Parkinson's disease. Parkinsonism Relat Disord 35:55-62

44. Espay AJ, Lang AE (2017) Common Myths in the Use of Levodopa in Parkinson Disease: When Clinical Trials Misinform Clinical Practice. JAMA Neurol 74:633-634

45. Verschuur CVM, Suwijn SR, Boel JA et al (2019) Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. N Engl J Med 380:315-324

46. Fasano A, Canning CG, Hausdorff JM, Lord S, Rochester L (2017) Falls in Parkinson’s disease: A complex and evolving picture. Mov Disord 32:1524-1536

47. Fraigne JJ, Torontali ZA, Snow MB, Peever JH (2015) REM Sleep at its Core - Circuits, Neurotransmitters, and Pathophysiology. Front Neurol 6:1-9

48. Del Tredici K, Braak H (2013) Dysfunction of the locus coeruleus – norepinephrine system and related circuitry in Parkinson’s disease-related dementia. J Neurol Neurosurg Psychiatry 84:774-783

49. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM (2017) Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson’s Disease: a cohort study. Lancet Neurol 16:66-75

50. Anang JB, Gagnon JF, Bertrand JA et al (2014) Predictors of dementia in Parkinson disease: a prospective cohort study. Neurology 83:1253-1260

51. Chaudhuri KR, Martinez-Martin P, Brown RG et al (2007) The Metric Properties of a Novel Non-Motor Symptoms Scale for Parkinson's Disease: Results From an International Pilot Study. Mov Disord 22:1901-1911

**FIGURE CAPTIONS**

**Fig 1 Distribution of benign and malignant Parkinson’s disease according to age at onset**

bPD: benign Parkinson disease (n= 210); mPD: malignant Parkinson disease (n= 155). \* Significant difference between bPD and mPD (p< 0.01)

**Fig 2 Smoking status, alcohol intake, and physical activity**

Smoking status, use of alcoholic beverages, and physical activity in bPD (n= 210) and mPD (n= 155) at baseline. bPD: benign Parkinson disease; mPD: malignant Parkinson disease. Significant difference between groups: \* p< 0.05; \*\* p< 0.001

**Fig 3 Distribution of clinical features according to age at onset**

RBD: Rapid Eye Movement Behavior Disorder; bPD: benign Parkinson Disease; mPD: malignant Parkinson disease; UPDRS: Unified Parkinson Disease Rating Scale. \*: Significant difference between bPD and mPD (p< 0.05). The numbers of patients considered in the analyses are reported in Tables 1 and 2

**Supplementary Fig 1 (Online Resource 1) Diagram showing the screening and inclusion processes**

bPD: benign Parkinson Disease; mPD: malignant Parkinson Disease. Br: Brescia; Ci: Cincinnati; Ki: Kiel; Ma: Madrid; Mi: Milan; Pi: Pisa; Ro: Rochester; To: Toronto; Tu: Turin

\*: number of bPD fulfilling the “10-year follow-up in patients with age at PD onset > 60 years-old” criterion