J Neurol (2017) 264:1583–1607
DOI 10.1007/s00415-016-8384-9

REVIEW

The relevance of gender in Parkinson's disease: a review

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Received: 28 November 2016 / Revised: 21 December 2016 / Accepted: 22 December 2016 / Published online: 4 January 2017

Abstract Since the official and systematic inclusion of sex and gender in biomedical research, gender differences have been acknowledged as important determinants of both the susceptibility to develop neurodegenerative diseases in general population and the clinical and therapeutic management of neurodegenerative patients. In this review, we gathered the available evidence on gender differences in Parkinson's disease (PD) regarding clinical phenotype (including motor and non-motor symptoms), biomarkers, genetics and therapeutic management (including pharmacological and surgical treatment). Finally, we will briefly discuss the role of estrogens in determining such differences. Several data demonstrate that PD in women starts with a more benign phenotype, likely due to the effect of estrogens. However, as the disease progresses, women are at higher risk of developing highly disabling treatment-related complications, such as motor and non-motor fluctuations as well as dyskinesia, compared with men. In addition, women have lower chances of receiving effective treatment for PD as deep brain stimulation. Taken together these findings challenge the definition of a more benign phenotype in women. Still, much work needs to be done to better understand the interaction between gender, genetics and environmental factors in determining the PD risk and clinical features. Improving our understanding in this field may result in implementation of strategies to identify prodromal PD and speed efforts to discern new directions for disease tailored treatment and management.

Keywords Parkinson · Gender · Motor · Non-motor · Genetic · Sex · Treatment · Surgery · Biomarker

Abbreviations

AUC	Area under the curve
F	Female
M	Male
LEDD	Levodopa equivalent daily dose
NMS	Non motor symptoms
PD	Parkinson's disease
UPDRS-III	Unified Parkinson's Disease Rating Scale part III

Introduction

According to the working definitions of sex and gender provided by the Institute of Medicine's Committee on Understanding the Biology of sex and gender differences, the term *sex* refers to the classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement, while the term gender refers to a person's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation [1]. However, these terms are not univocal and cannot always be used in a mutually exclusive fashion. Thus, since gender is rooted in biology and shaped

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by environment and experience [1], gender rather than sex is more appropriate to define the interaction of biological and social elements affecting health outcomes [1].

Sex differences in brain structure and function initiate through sex determining genes and fetal hormonal programming and have important implications for brain-based disease risk; then, sex-specific genetic and hormonal factors, as well as age-related physical changes further contribute to biological differences in expression of neurodegenerative diseases, including Parkinson's disease (PD) [1]. In addition, a variety of broader societal factors, including role expectations and social attitudes, also have roles in the risk, course and outcome of neurodegenerative diseases. As a matter of fact, a range of behavioral and lifestyle choices associate with gender differences, including diet, exercise, smoking and caffeine are emerging as potential modifiers of the PD risk during life [2].

Since the official and systematic inclusion of sex and gender in biomedical research [3], gender differences have been acknowledged as important determinants of both the susceptibility to develop neurodegenerative diseases in general population and the clinical and therapeutic management of neurodegenerative patients [4].

The aim of this review is to gather the available evidence on gender differences in PD regarding clinical phenotype (including motor and non-motor symptoms), biomarkers, genetics and therapeutic management (including pharmacological and surgical treatment). Before the closedown, we will briefly discuss the role of estrogens in determining such differences. However, since our approach is mainly clinical, we will not include in the present review all the preclinical data available on the topic.

Indeed, improving our understanding in this field may result in implementation of strategies to identify prodromal PD cases and speed efforts to discern new directions for PD tailored treatment and management.

Methods

The authors searched personal files and PubMed for peer-reviewed articles published in English language with no time limits. The search terms "agonist", "biomarker", "deep brain stimulation", "epidemiology", "gender", "genetic", "kinetic", "levodopa", "men", "motor features", "non-motor features", "Parkinson", "sex", "surgery", "weight" and "women" were used. Additional articles were identified by searching the reference lists of identified reviews that provided insightful or comprehensive overviews on gender differences in PD. The studies and meta-analysis considered in this review are detailed in Table 1.

Epidemiology and phenotypic differences

Epidemiology

Confirming previous data [5], a meta-analysis including 17 relevant studies and over 2500 PD cases, determined an overall age-standardized incidence M:F ratio of 1.46 (95% CI 1.24–1.72) [6]. This meta-analysis also disclosed a high-level heterogeneity between included studies and a positive relationship between age of onset and M:F incidence ratio [6, 7]. As for prevalence, a meta-analysis including data published between 1985 and 2000 reported a significant difference in gender ratio for individuals from 50 to 59 years old, with a PD prevalence of 41/100.000 in women and 134/100.000 in men ($p < 0.05$) [8]. When stratified by geographic location, M:F prevalence ratios were in favour of men in both the Western countries and South America, but not in Asia, although methodological issues may account for such discrepancy [8].

By analyzing the Health Insurance drugs reimbursement databases, a recent French nationwide study largely confirmed previous data reporting an overall M:F incidence ratio of 1.49 (95% CI 1.41–1.57, $p < 0.001$) and an overall M:F prevalence ratio of 1.48 (95% CI 1.45–1.51, $p < 0.001$) [9]. Both M:F incidence and prevalence ratios were markedly influenced by age in a strikingly progressive pattern, with incidence increasing by 0.14 per 10-year age increment and prevalence increasing by 0.05 for every 10-year age increment. As expected, this pattern was more pronounced for incidence than prevalence ratios, since the latter is most likely affected by gender differences in survival [9]. Indeed, male sex is associated with an increased mortality rate in PD for two complementary reasons [10–12]. First, it is the reflexion of the overall shorter life expectancy of men in the general population. Then, the factors usually predicting higher mortality in PD, as cognitive impairment and higher postural instability and gait scores, are much more common in men [10–12].

Motor symptoms

By examining a clinic-based cohort of 253 subjects, Haaxma et al. first delineated phenotypic gender differences in a large sample of PD patients [13]. Key findings of this study were: (a) women were 2 years older than men at symptom onset and presented more likely with tremor (67%) than men (48%); (b) tremor dominance was associated with a slower decline on motor scales; (c) at symptoms onset, women had 16% higher striatal $^{[123I]}$FP-CIT binding than men; (d) in women, age at onset correlated positively with parity, age at menopause and fertile life span [13]. Taken together, these findings suggest a more benign phenotype in women with PD possibly related

Table 1 Studies and meta-analyses focused on gender differences in Parkinson's disease included in the review

Study	Type of study	Aim(s) of the study	No. of PD patients (Men, %)	Age of PD patients,* years	Disease duration,* years	Main findings
Epidemiology						
Lonneke [10]	5-year prospective, hospital-based study (part of the PROPARK cohort, the Netherlands)	To identify motor and non-motor features predicting mortality in PD	414 (64)	61.14 (11.37)	10.62 (6.53)	49 (11.8%) patients died Male sex, older age and higher PIGD score, cognitive impairment and psychotic symptoms predicted decreased survival
Moisan [9]	French nationwide study based on national drugs databases (French National Health Insurance)	To investigate sex differences in PD frequency and conduct a meta-analysis of the available literature	188.562 (NA)	NA	NA	M:F ratios were 1.48 (95% CI 1.45–1.51, $p < 0.001$) for prevalence and 1.49 (95% CI 1.41–1.57, $p < 0.001$) for incidence M:F incidence and prevalence ratios increased with age, with incidence increasing by 0.14 per 10-year age increment and prevalence increasing by 0.05 for every 10-year age increment The meta-analysis including 22 incidence studies (14.126 cases, 46% women) confirmed that M:F ratios increase with age (0.26 per 10 years, $p = 0.005$)
Pinter [11]	38-year prospective study (Austria)	To identify predictors of mortality in PD	237 (NA)	NA	NA	230 (97%) patients died Male sex, gait disorders and absence of tremor or unequivocal asymmetry at onset predicted mortality
Pringsheim [8]	Meta-analysis including 47 door-to-door or population-based prevalence studies	Systematic review of PD prevalence studies worldwide	2.019 PD out of 4.665.742 of subjects considered	NA	NA	PD prevalence rises with age Male predominance is present in all age groups but is significant in the 50-59 age group (F = 41/100.000; M = 134/100.000) M:F prevalence ratios were in favour of men in both the Western countries and South America, but not in Asia
Taylor [6]	Meta-analysis including 14 studies	Systematic review of PD incidence studies	2.557 (NA)	70.6	NA	Incidence M:F ratio of 1.46 (95% CI 1.24–1.72)
Wooten [5]	Meta-analysis including 7 studies	To review the gender differences in PD incidence studies	1.837 (51.95)	NA	NA	M:F weighted mean incidence = 1.49
Xu [12]	Meta-analysis including 8 studies	To evaluate mortality risk and predictors in PD	718 PD deaths and 13.660 healthy controls (HC) deaths	NA	NA	PD had a greater risk of all-cause mortality (RR = 2.22; 95% CI 1.78–2.77) PD patients with dementia had higher mortality risk (RR = 3.78; 95% CI 2.06–6.92) Male gender was associated with higher mortality rates (RR = 2.05;95% CI 1.36–3.08)

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Motor symptoms						
Bjornestad [18]	5-year prospective, longitudinal population-based study (Multicenter, Norway)	To determine the incidence, risk factors, evolution, and treatment of motor fluctuations and dyskinesias	189 (60.3)	67.7 (9.3)	2.3 (9.3)	The 5-year cumulative incidence of motor complications was 52.4% Motor fluctuations occurred in 42.9% and levodopa-induced dyskinesias (LID) in 24.3% Severer motor scores predicted both motor fluctuations ($p = 0.016$) and LID ($p < 0.001$), lower age at diagnosis predicted motor fluctuations ($p = 0.001$), whereas female gender predicted LID ($p = 0.001$) irrespective to body weight

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Cereda [14]	Cross-sectional study (Italy)	To investigate the potential effect of reproductive factors on the clinical features of PD	579 (0)	68.5 (9.9)	5 (range 2–9)	Age at PD onset was positively associated with age at menarche and at menopause, length of fertile life and duration of estrogen exposure UPDRS motor score was inversely associated with age at menopause, length of fertile life and duration of estrogen exposure Increasing age at menarche was also associated with predominant resting tremor at PD onset
Colombo [19]	Cross-sectional study (Multicenter, Italy)	To evaluate gender differences in wearing off	617 (61.8)	66.8 (9.2)	<5 years: 185 >5 years: 432	Prevalence of wearing off was higher among women, according to both neurologists' judgment and the WOQ-19
Haaxma [13]	Longitudinal, prospective study (the Netherlands)	To investigate gender differences in disease characteristics, motor deterioration and nigrostriatal degeneration	253 (62)	53.7 (range 28–79)	2.6 (range 2–10)	Age at onset was 2.1 years later in women (53.4 years) than in men (51.3 years) In women, age at onset correlated positively with parity, age at menopause and fertile life span Women presented more often with tremor (67%) than men (48%) Overall, patients presenting with tremor had a 3.6 year higher age at onset and a 38% slower UPDRS-III deterioration Women had a 16% higher striatal [123I]FP-CIT binding than men at symptom onset and throughout the course of PD
Hassin-Baer [22]	Historical prospective study (Israel)	To identify factors associated with time to appearance of levodopa-induced dyskinesia	155 (58.1)	NA	NA	Patients with LID (57.4%) were significantly younger at disease onset than those without Female gender was associated with a shorter time to LID and the median time to LID was 6 years for males and 4 years for females ($p = 0.004$)
Sato [17]	Retrospective study (Japan)	To report long-term outcomes of PD Japanese patients	1.768 (44.8)	66.1 (10.1)	9.4 (6.2)	Time to reach H&Y = III was slightly but significantly shorter in women ($p < 0.001$) Time to develop wearing off and LID was shorter in women compared to men
Saunders-Pullman [16]	Retrospective study (USA)	To determine whether there are gender discrepancies in diagnosis and time to present to a movement disorder specialist	109 (51.3)	63.5 (range 54.9–70)	1.9 (range 1.1–4.1)	The expected duration from onset to movement disorder specialist visit for women was 61% greater than for men in the unadjusted model ($p = 0.002$)

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Zappia [20]	Cohort study (Italy)	To examine clinical and genetic risk factors for individual susceptibility of peak-dose dyskinesia	215 (57.2)	66.6 (8.6)	8.7 (5)	115 patients (48.8%) exhibited peak-dose dyskinesia following short-term levodopa administration, and 110 patients (51.2%) did not In the whole sample predictors for the occurrence of LID were: female sex (OR 3.29; 95% CI 1.76–6.17), earlier age at onset (OR 1.05; 95% CI 1.02–1.09) duration of LD treatment (OR 1.1; 95% CI 1.02–1.19) LD dosage (OR 1.001; 95% CI 1–1.003) In men predictors for the occurrence of LID were: earlier age at onset (OR 1.08; 95% CI 1.03–1.13), LD dosage (OR 1.002; 95% CI 1–1.003), CAnSTR genotype (OR 0.34; 95% CI 0.14–0.84) and body weight <61 kg (OR 7.64; 95% CI 1.36–42.92) In female only earlier age at onset was best predictor the occurrence of peak-dose dyskinesia (OR 1.07; 95% CI 1.02–1.13; $p = 0.008$)
Non-motor symptoms						
Anang [39]	Prospective cohort study (Canada)	To investigate a set of possible markers of early dementia in PD	80 (63.7)	66.2 (10.9)	5.7 (4.2)	27/80 (34%) developed dementia Predictors of dementia were: male gender (OR = 3.64, $p = 0.023$), baseline mild cognitive impairment (OR = 22.5, $p = 0.001$), RBD (OR = 49.7, $p = 0.001$); higher baseline blood pressure (OR = 1.37 per 10 mm Hg, $p = 0.032$), orthostatic blood pressure drop (OR = 1.84 per 10 mm Hg, $p = 0.001$); abnormal color vision (OR = 3.3, $p = 0.014$)
Augustine [129]	Cross-sectional analysis of a multicenter clinical trial (NET-PD)	To examine gender differences in clinical features and disease severity	1.741 (62.5)	Range 30–80	1.7 (1.8)	Women had better performance compared to men on the SCOPA-COG ($p < 0.0001$) and the Symbol Digit Modality measures ($p < 0.0001$)
Cereda, 2016 [41]	Cross-sectional, retrospective study (Italy)	To investigate the relationship between dementia and gender along with other risk factors, such as age and disease duration	6.599 (58.3)	68.4 (10.1)	8.6 (6.4)	Prevalence of dementia was 11.5% (95% CI 10.8–12.3) Age, disease duration and male gender independently predicted dementia While the rate of dementia increased in males over all age strata, females prevalence began to increase steadily after the age of 65 years, reaching male estimates only after 80 years of age
Fengler [130]	Cross-sectional, retrospective study (Multicenter, Germany)	To investigate gender differences in cognitive tests	656 (67.8)	67.5 (7.8)	6.8 (5.4)	Raw-score analysis showed that PD women scored higher in verbal memory (word list learning, $p = 0.02$; recall, $p = 0.03$), while men outperformed women in visuoconstruction ($p = 0.002$) and tests evaluating recall of figures ($p = 0.005$) Gender-corrected Z scores showed that men scored higher in verbal memory (word list learning, $p = 0.02$; recall, $p = 0.02$; recognition, $p = 0.04$), while no difference was found for visuospatial tests

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Gao [131]	Cross-sectional study (China)	To investigate gender differences in cognitive performances	311 (55.3)	60.8 (11.3)	3.8 (5)	Montreal Cognitive Assessment (MoCA) scores were higher in men ($p < 0.05$) Men had better performances in visuospatial function, naming and abstraction ($p < 0.05$) Women had lower scores in information, vocabulary, picture completion, block design and picture arrangement ($p < 0.05$)
Guo [36]	Cross-sectional study (China)	To evaluate gender- and age-related differences in non-motor symptoms in Chinese patients	522 (56.7)	61.6 (11.4)	4.4 (4.1)	Women had more frequently NMS in sleep/fatigue, mood/apathy domain and pain symptoms Men had more frequently urinary symptoms
Leentjens [23]	Cross-sectional study (International multicenter study)	To describe the frequency and symptoms anxiety disorders, as well as to identify their risk factors in a PD population	340 (61)	64.8 (9.2)	8.2 (5.5)	34% of subjects met the DSM-IV criteria for at least one anxiety disorder; 11.8% met criteria for multiple anxiety disorders; and 11.4% had clinically relevant anxiety symptoms without meeting the criteria for any specific anxiety disorder Female sex, the presence of motor fluctuations, as well as a previous history of an anxiety disorder were markers for anxiety disorders
Leentjens [24]	Cross-sectional study (International multicenter study)	To construct a model for depression in PD and to study the relative contribution of PD-specific and nonspecific risk factors to this model	340 (61%)	64.8 (9.2)	8.3 (5.6)	Three PD-specific variables (increased disease duration, more severe motor symptoms, the use of levodopa) and 6 non-specific variables (female sex, history of anxiety and/or depression, family history of depression, worse functioning on activities of daily living, and worse cognitive status) were significantly associated with depression Non-specific risk factors had a 3-times higher influence in the model than PD-specific risk factors
Liu [34]	Cross-sectional study (International multicenter study-PPMI cohort)	To examine potential sex differences in non-motor symptoms, and to identify symptoms that can best differentiate patients with early PD from HC	PD: 414 (64.9) HC: 188 (64.3)	PD: 62.1 (9.8) HC: 61.7 (10.9)	6.3 (6) months	Male PD patients had more pronounced deficits in olfaction ($p = 0.02$) and in certain cognitive measurements (all $p < 0.01$) than female patients Female PD patients experienced higher trait anxiety ($p = 0.02$) The combination of the University of Pennsylvania Smell Identification Test (UPSIT), MoCA, Scales for Outcomes in Parkinson's Disease–Autonomic (SCOPA-AUT), and state anxiety from the State-Trait Anxiety Inventory effectively differentiated patients with PD from HC UPSIT, MoCA, and SCOPA-AUT predicted PD diagnosis in men UPSIT, MoCA, and RBD Screening Questionnaire predicted PD diagnosis in women

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Martinez-Martin [27]	Cross-sectional study (International multicenter study)	To determine the difference by gender in the frequency and severity of a range of non-motor symptoms	951 (62.6)	64.4 (9.9)	7.9 (5.7)	Fatigue, feelings of nervousness, feelings of sadness, constipation, restless legs, and pain were more common and severe in women Daytime sleepiness, dribbling saliva, interest in sex, and problems having sex were more prevalent and severe in men Regarding the NMS domains, Mood/Apathy and Miscellaneous problems (pain, loss of taste or smell, weight change, and excessive sweating) were predominantly affected in women and sexual dysfunction in men
Nicoletti [42]	Case–control, cross-sectional (multicenter, Italy)	To evaluate gender differences in NMS prevalence in PD and in comparison with HC	PD: 585 (59.5) HC: 481 (34.9)	PD: 66.8 (9.8) HC: 63.4 (10.1)	7.2 (5.6)	All NMS were more frequent in PD than HC; PD women showed higher frequency of depression and urinary disturbances than men With respect to the control population, according to logistic regression stratified by sex and adjusted by age, PD men showed a stronger positive significant association with almost all NMS compared to women, excepting for urinary disturbances The strongest association among PD men was recorded for cognitive impairment (adjusted OR 5.44 for men and 2.82 for women) and depression (adjusted OR 30.88 for men and 12.72 for women)
Picillo [29]	Cross-sectional study (Italy)	To assess gender effect on the prevalence of non-motor symptoms in a large cohort of early, drug-naïve PD patients compared with age and sex-matched HC	PD: 200 (63) HC: 93 (64.5)	PD: 61.3 (8.8) HC: 60.7 (7.8)	11.5 (9.5) months	Male PD patients complained of problems having sex and taste/smelling difficulties significantly more frequently than female PD patients Men with PD complained more frequently of dribbling, sadness/blues, loss of interest, anxiety, acting during dreams, and taste/smelling difficulties compared to HC men Female PD patients reported more frequently loss of interest and anxiety as compared with HC women
Picillo [35]	2-year prospective study (Italy)	To assess gender-related differences in non-motor symptoms before and after starting dopaminergic therapy in newly diagnosed PD patients	134 (64.2)	63 (8.6)	38.7 (11.3) months	Sadness/blues presented a significant percentage reduction compared to baseline in both sexes Urgency, daytime sleepiness, weight gain and sex drive presented a significant percentage increase only in men Occurrence of weight gain was related to therapy in both sexes Male gender was a risk factor for dribbling and nocturia, irrespective of therapy and clinical features

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Picillo [37]	4-year prospective study (Italy)	To assess the relationship between non-motor fluctuations and gender along with other potential risk factors	47 (65.9)	60.7 (8.4)	14 (5.6) months	Female gender was associated with non-motor fluctuations (OR = 5.33,95% CI 1.21–23.4, $p = 0.027$) Women had greater likelihood of developing higher WOQ-19 Non-motor scores (OR = 4.58, 95% CI 1.23-17.03, $p = 0.023$) Notwithstanding, no gender differences were detected in medication intake
Pigott [40]	6-year longitudinal prospective study (USA)	To report the rates and predictors of progression from normal cognition to either mild cognitive impairment or dementia	141 (63)	68.6 (7)	5 (4.4)	The cumulative incidence of cognitive impairment was 8.5% at year 1 and 47.4% by year 6 In a multivariate analysis, predictors of future decline were male sex ($p = 0.02$), higher UPDRS motor score ($p \leq 0.001$), and worse global cognitive scores ($p < 0.001$)
Scott 2000 [132]	Postal survey (Sweden)	To evaluate gender differences in symptoms severity and progression	948 (62.2)	66 or older	11.1	At symptom onset, women reported neck-pain and low back pain more frequently than men At the time of the evaluation, writing difficulties, fumblingness, gait problems, speech problems, increased saliva, lack of initiative were more common in men
Solla [26]	Cross-sectional study (Italy)	To assess gender differences in motor and non-motor symptoms	PD: 156 (58.3) HC: 132 (61.3)	PD: 69.3 (8.5) HC: 69.8 (8.1)	6.3 (4.4)	Women presented more frequently with tremor as initial symptom ($p < 0.025$) and worse UPDRS instability score ($p < 0.02$) Non-Motor Symptoms Scale (NMSS) score in women with PD was significantly higher than that in men ($p < 0.018$) Women with PD had higher scores in cardiovascular ($p < 0.002$), sleep/fatigue ($p < 0.018$) and mood/apathy ($p < 0.001$) domains and had more frequently fatigue ($p < 0.03$), lack of motivation ($p < 0.015$) and sadness ($p < 0.009$) Men with PD reported higher scores in the sexual dysfunction domain ($p < 0.017$) and complained more frequently altered interest in sex ($p < 0.001$) and compulsive sexual behavior ($p < 0.001$)
Song [30]	Cross-sectional study (China)	To investigate gender differences on motor and non-motor symptoms in de novo patients	428 (60.3)	60.6 (10.7)	1.9 (1.7)	Women had more depressive symptoms Men had higher scores for Mini Mental State Examination (MMSE) No significant differences were found for other NMS
Szewczyk-Krolikowski [25]	Cross-sectional study (Multicenter study, UK)	To delineate effects of age and gender on PD phenotype in an incident cohort PD patients and HC from the Oxford Parkinson Disease Centre (OPDC)	PD: 490 (62.4) HC: 176 (36.4)	PD: 67.9 (9.3) HC: 64.3 (9.1)	3.3 (2.4)	Men presented increased severity and greater symptom symmetry in the face, neck and arms Women had more postural problems Men had more severe cognitive impairment, greater rate of RBD, more orthostatic hypotension and sexual dysfunction

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Uc [38]	5-year longitudinal prospective study (International Multicenter study-DATATOP cohort)	To investigate the incidence and risk factors of cognitive impairment	740 (66.5)	61.4 (9.6)	2.2 (1.3)	2.4% had cognitive impairment at 2 years and 5.8% at 5 years Cognitive impairment was associated with older age, hallucinations, male gender, increased symmetry of parkinsonism, increased severity of motor impairment (except for tremor), speech and swallowing impairments, dexterity loss, and presence of gastroenterologic and urologic issues at baseline
Wee [133]	18-month longitudinal, prospective study (Singapore)	To examine the factors that predict individual trajectories of apathy	89 (73)	65.4 (7.8)	5.2 (3.8)	At baseline, apathy was present in 42.7% Male gender, lower educational attainment, higher depression symptom severity, more severe functional disability and the presence of dyskinesias at baseline predicted increasing apathy over the subsequent 18 months
Biomarkers						
Ascherio [48]	2-year longitudinal prospective study (International multicenter-DATATOP cohort)	To determine whether serum urate predict disease progression	774 (65.9)	62 median	<5	Increasing urate predicted lower UPDRS change and less need for levodopa more in men than in women with PD
Brighina, 2010 [43]	Cross-sectional (Italy)	To measure α-synuclein protein in lymphomonocytes in PD patients and HC	PD: 78 (60.2) HC: 78 (57.7)	PD: 65.1 (9.4) HC: 48.8 (18.2)	4 (range 2–8)	alpha-synuclein levels were not significantly different between PD and HC In HC, alpha-synuclein protein levels increased with age and were higher in men than in women
Caranci [45]	Cross-sectional (Italy)	To compare total α-synuclein plasma concentrations in PD patients and age-matched HC	PD: 69 (57.9) HC: 110 (51.8)	PD: 65.2 (9) HC: 64.8 (8)	10 (median)	Plasma alpha-synuclein were decreased in patients in advanced stage in men, but not in women Plasma alpha-synuclein concentration was associated with cognitive impairments, hallucinations, and sleep disorders only in men
Gao [52]	Nested case–control study (Multicenter, USA)	To examine whether higher plasma urate concentrations are associated with a lower risk of PD and whether there is a sex difference in the potential urate–PD relationship	PD: 388 (52) HC: 1.267 (35)	PD: NA HC: 60.7	NA	Higher baseline urate was associated with lower PD risk in men (RR: 0.59, 95% CI 0.35–0.99, $p = 0.018$), but not in women (RR: 1.06, 95% CI 0.66–1.71, $p = 0.38$) A meta-analysis including further 325 PD cases from 3 ongoing US prospective studies confirmed the relationship between PD risk and urate in men (RR: 0.63,95% CI 0.42 to 0.95, $p = 0.03$), but not in women (RR: 0.89, 95% CI 0.57–1.40, $p = 0.52$)
Ho [46]	Cross-sectional study (Korea)	To compare levels of LRRK2, α-synuclein, and DJ-1 in urine exosomes from PD patients and HC	PD: 26 (53.8) HC: 21 (47.6)	PD: 73 (2.1) HC: 70 (3.2)	5.8 (0.6)	No difference in LRRK2, alpha-synuclein, and DJ-1 urine exosomes in PD compared to HC DJ-1 urine exosome level was significantly higher (1.7-fold) and age-related in men with PD than in HC
Ikeda [44]	Cross-sectional study (Japan)	To compare serum urate, paraoxonase-1, iron, ferritin and lipid in PD patients and HC	PD: 119 (47) HC: 120 (50)	PD: 73.4 (8.7) HC: 72.9 (8.8)	6.9 (5.1)	Serum levels of total cholesterol and low density lipoprotein-cholesterol were inversely related to PD stage and duration in women

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Jain [134]	Community-based cohort (Multicenter, USA)	To investigate the relationship between serum urate and PD risk	PD: 154 HC: 5.749 (39.5)	PD: 72.8 HC: 73 (5.6)	NA	Urate concentrations were lower in women than men [316.8 (88) µmol/l versus 367.4 (87.7) µmol/l, $p < 0.0001$] and in women no association between urate and PD risk was observed In men, the PD risk was significantly increased for urate <300 µmol/l (OR: 1.69, 95% CI 1.03–2.78)
Jesus [50]	Cross-sectional study (Spain)	To investigate whether urate is related to clinical parameters of the disease	PD: 161 (55.9) HC: 178 (60.6)	PD: 63.2 (11.9) HC: 60.5 (13.6)	9 (6.6)	Severity of PD was related to urate when considering both sexes or men only but not in women only LEDD was inversely associated with urate levels in men only
McFarland [51]	Postmortem study (USA)	To explore weather lower urate in brain is associated with PD	PD: 17 (47) HC: 13 (61.5)	PD: 79.2 (7.5) HC: 78.3 (11.3)	NA	Urate levels in cortical and striatal tissue trended lower in PD compared to controls in males only
Schwartzschield [47]	Longitudinal study (Multicenter—PERCEPT cohort)	To determine whether serum urate predicts prognosis	804 (64.3)	59 (median)	<5	Increased baseline urate reduce the need for dopaminergic treatment This association was markedly stronger in men (HR = 0.39; 95% CI 0.26–0.60; $p < 0.0001$) than in women (HR = 0.77; 95% CI 0.39 to 1.50; $p = 0.4$) The percent loss in striatal [123 I]β -CIT uptake also improved with increasing serum urate concentrations (overall p for trend = 0.002; men, $p = 0.0008$; women, $p = 0.4$)
Schwartzschield [49]	Cross-sectional study (Multicenter-PERCEPT cohort)	To investigate whether higher levels of urate is a predictor of having a dopamine transporter brain scan without evidence of dopaminergic deficit	797 (63.9)	59.4 (11.6)	<5	Odds of having a scan without evidence of dopaminergic deficit rose across increasing quintiles of urate level, with an age and gender-adjusted odds ratio of 3.2 comparing the highest to the lowest urate quintile (95% CI 1.5 to 7.2; p for trend = 0.0003) The association was significant in men but not in women, regardless of whether common or sex-specific quintiles of urate were used
Genetics						
Agalliu [67]	Cross-sectional (International multicenter study)	To examine the association between LRRK2 G2019S mutation and cancer among PD patients	1.549 (56.1)	70.9 (10.8)	9.8 (7)	177 (11.4%) LRRK2 G2019S mutation carriers were identified Mutation carriers were younger at PD diagnosis and more likely to be women (53.1%) and of Ashkenazi Jewish descent (76.8%) in comparison with non-carriers
Cilia, 2014 [68]	Cross-sectional study (Italy)	To investigate whether or not LRRK2 status influences gender distribution and PD phenotype	2.392 (59.2)	65.6 (9.9)	11.9 (6.5)	LRRK2 mutations were identified in 40 PD patients (1.6%) No major clinical differences were found between LRRK2-carriers and non-carriers Female gender was more common amongst carriers than non-carriers (57% vs. 40%; p = 0.01), without any gender-related difference in clinical features

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Clark [69]	Cross-sectional study (USA)	To evaluate the frequency of LRRK2 mutations in PD	PD: 504 (60.3) HC: 314	PD: 60.8 (11.5)	7.8 (6)	LRRK2 G2019S mutation was present in 28 cases with PD (5.6%) and 2 HC (0.6%) (OR: 9.18, 95% CI 2.17 to 38.8, $p < 0.01$) Mutation carriers were more frequently women compared to non-carriers (60.7% versus 38.4%, $p = 0.03$)
Foltynie [53]	Cross-sectional study (UK)	To investigate the impact of BDNF Val/Met polymorphisms on frontal tasks in PD patients	291 (60.4)	59.4	NA	Patients with low rates of BDNF secretion (Met alleles) performed significantly better in frontal tasks than those with high rates of secretion (Val alleles) Subgroup analyses revealed that the effect is most apparent in women and among patients with prior dopaminergic exposure
Gan-Or [74]	Meta-analysis including 17 case–control studies	To conduct a sex-stratified meta-analysis, examining whether the genetic data support the hypothesis of a sex effect in LRRK2-associated PD	24.088 (58.7)	NA	NA	A total of 1080 LRRK2-associated PD patients were identified Among men, LRRK2 mutation carriers had a pooled OR for PD of 4.20 (95% CI 2.95–5.99, $p < 0.0001$) and among women, LRRK2 mutation carriers had a pooled OR for PD of 4.73 (95% CI 3.26–6.86, $p < 0.0001$) The M:F ratio was 1.02: 1.00 (50.6% men and 49.4% women)
Gatt [54]	Cross-sectional study (International multicenter study)	To verify if mitochondrial transcriptor factor A SNP rs2306604 genotype frequencies are associated with PDD	PDD: 63 HC: 56	NA	NA	Mitochondrial transcriptor factor A SNP rs2306604 genotype frequencies in the PDD male group were significantly different from the male controls ($p = 0.002$) Homozygosity for the A allele was strongly associated with an increased risk of PD in males (OR = 5.570, $p = 0.001$,) compared with AG/GG carriers
Gusdon [55]	Cross-sectional study (China)	To determine whether mt-ND2 5178A/C polymorphism is associated with a reduced PD risk	PD: 484 (54.6) HC: 710 (46.7)	PD: 60.6 (10.1) HC: 68.4 (10.6)	NA	There was no significant association between mt-ND2 5178A/C polymorphism and PD when analyzing the entire population Subgroup analysis revealed that in males the frequency of 5178A was significantly lower in PD patients (20.0% versus 27.7%, $p = 0.027$)
Klebe [56]	Cross-sectional study (International multicenter study)	To test whether the Val158Met polymorphism is a modifier of the age at onset in PD	PD: 5.886 (sex ratio: 1.5) HC: 10.723 (sex ratio: 1.01)	PD: 57.6 (13.8) HC: 60 (10.1)	NA	The distribution of the COMT polymorphism was not different in patients and controls ($p = 0.22$) Patients with the Val/Val had younger age at onset (57.1 ± 13.9, $p = 0.03$) than the Val/Met (57.4 ± 13.9) and the Met/Met genotypes (58.3 ± 13.5) The difference was greater in men (1.9 years between Val/Val and Met/Met, $p = 0.007$) than in women (0.2 years, $p = 0.81$)

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Lin [57]	Cross-sectional study (Taiwan)	To investigate the association of a1-antichymotrypsin gene polymorphism and PD	PD: 210 (sex ratio 1.14) HC: 260 (sex ratio 1.15)	PD: 63.6 (11.5) HC: 63.7 (11.1)	5.2 (4.9)	No differences of allelic frequency (A and T) and genotype polymorphism (AA, AT and TT) of the a1-antichymotrypsin gene in PD patients and HC There were significantly fewer early-onset PD (onset age younger than 60 years) or PD women carrying the homozygote AA genotype (a1-antichymotrypsin-AA) than HC ($p = 0.046$ and 0.044, respectively) Reduced risk of a1-antichymotrypsin -AA was particularly significant among PD women with age at onset younger than 60 years (OR: 0.796, 95% CI 0.749–0.847, $p < 0.0001$)
Lin [58]	Cross-sectional study (Taiwan)	To evaluate a possible relationship between the pCD14 polymorphism and the risk of PD	PD: 200 (56) HC: 200 (56)	PD: 64.5 (11.3) HC: 64.5 (6.6)	5 (4.7)	Results revealed that the CD14-T allele of the pCD14 polymorphism was different in female PD patients compared to female controls (OR = 1.262, $p = 0.038$), but no difference was found in males. Female individuals with homozygote CD14-TT genotype had increased PD risk of 1.28 time ($p = 0.027$)
Liu [59]	Cross-sectional study (China)	To investigate the association between CCDC62 rs12817488 and PD	PD: 341 (52.2) HC: 423 (53.4)	NA	NA	CCDC62 rs12817488 A allele is associated with PD diagnosis ($p = 0.006$) in Chinese population The association of rs12817488 with PD was only found in females
Mariani [60]	Cross-sectional study (Italy)	To verify the role of iron status in PD	PD: 92 (67.4) HC: 358 (35.8)	PD: 70 median (range 30-83) HC: 62 median (range 31–87)	7 (4.5)	No significant differences in the D544E and R793H variants of the ceruloplasmin gene, the P589S variant of the transferrin gene, and the H63D and C282Y variants of the human hemochromatosis protein gene between patients and HC When the effect of sex was considered in the statistical model, an increase of the probability of having PD is associated with low iron concentration and transferrin-saturation
Orr-Urtreger [70]	Cross-sectional study (Israel)	To assess the occurrence of the LRRK2 mutations in Jewish Israeli PD patients	PD: 427 (64.2) HC: 1.802 (NA)	PD: 67.6 (10.2) HC: range 20–45	NA	Women were significantly over-represented among the G2019S mutation carriers
Palacios [61]	Nested case–control study (Multicentric, USA)	To examine associations between polymorphisms of caffeine metabolizing genes (CYP1A2 and NAT2) and PD risk	PD: 298 (46.6) HC: 1285 (43.6)	NA	NA	The CYP1A2 rs762551 (part of the cytochrome P450 system) polymorphism (lower enzyme inducibility) was marginally associated with an increased risk of PD (RR = 1.34; 95% CI 1.02, 1.78) in women, but not in men

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
San Luciano [62]	Cross-sectional study (USA)	To test weather the 174G > C (rs1800795) single nucleotide polymorphism (SNP) in the promoter of the interleukin-6 (IL6) gene and the 1730G > A (rs4986938) SNP in the estrogen receptor beta (ESR2) may influence the PD risk	PD: 380 (both Ashkenazi Jewish and non-Jews) HC: 522	NA	NA	The G allele of the −174G>C SNP was more common in Jewish PD cases ($p = 0.033$) as well as in non-Jewish men with PD ($p = 0.022$) The GG genotype increased the risk of PD by over twofold in non-Jewish men (OR = 2.11, 95% CI 1.14–3.89, $p = 0.017$), and approached significance in the total Jewish group with PD (OR = 1.42, 95% CI 0.97–2.06, $p = 0.067$) The A allele of the ESR2 1730G>A SNP was associated with a decreased risk for PD in Jewish women
Saunders-Pullman [71]	Cross-sectional study (USA)	To test whether there is an increased genetic component in women of Jewish background and assess whether parkinsonism is more frequent in family members of women with PD in comparison with family members of men with PD, adjusting for LRRK2 G2019S mutations in the proband	PD: 177 (52.5)	66.6 (11.6)	NA	Using Cox proportional hazards models to evaluate the risk of parkinsonism among family members of PD subjects, having a daughter with PD compared with a son was associated with increased risk of parkinsonism in the parent (HR 2.59, $p = 0.014$) as was having a child with a LRRK2 G2019S mutation (HR 3.19, $p = 0.003$) The increased risk among parents of women with PD persisted when adjusting for LRRK2 status (HR 2.19, $p = 0.023$)
Siminuvic [63]	PD: 10 (70) HC: 9 (66.6)	To determine gender differences in the gene expression profiles of dopamine neurons	NA	NA	NA	Different patterns of deregulation between males and females with more prominent downregulation of genes related to oxidative phosphorylation, apoptosis, synaptic transmission and transmission of nerve impulse in the male PD population
Yu [64]	Cross-sectional study (China)	To evaluate the possible association between rs12817488 polymorphism in the CCDC62/HIP1R gene and PD	PD: 515 HC: 518	NA	NA	The rs12817488 polymorphism in the CCDC62/HIP1R gene is associated with PD ($p = 0.003$) and that the genotype and allele frequencies are prevalent late-onset PD patients and male controls ($p = 0.025$ and $p = 0.007$, respectively)
Zhang [65]	Cross-sectional study (China)	To investigate the relationship between NCAPD2 polymorphisms and the risk of PD	PD: 265 (58.9) HC: 269 (59.9)	NA	NA	The A allele of rs7311174 and the T allele of rs2072374 of the NCAPD2 gene reduced PD risk in male patients ($p = 0.016$ and $p = 0.019$, respectively)
Zhao, 2015 [66]	Cross-sectional study (China)	To evaluate whether genetic polymorphisms of the TLR4 gene are associated with PD susceptibility	PD: 380 (62) HC: 380 (60.2)	PD: 62.5 (10.8) HC: 70.4 (8.2)	4.4 (3.6)	The frequency of rs1927914 C allele of the TLR4 gene was significantly reduced in male PD compared to male HC (OR = 0.714, 95% CI 0.549–0.929, $p = 0.012$)
Differences in management: pharmacological treatment						
Arabia [85]	Consecutive, clinic- based cohort study (Italy)	To examine the relationship between body weight and levodopa pharmacokinetic	164 (55.5) (65 PD patients with LID)	65.5 (8.9)	83.7 (59.8)	Body weight was inversely correlated with levodopa area under the curve (AUC) and half-life ($T_{1/2}$) ($p < 0.001$ and $p < 0.001$) Women were lighter than men (65.3 versus 73.9 kg, $p < 0.001$), more dyskinetic (53.4 versus 28.6%, p 0.001) and had greater AUC values (6.45 versus 4.94 μmol/l h, $p = 0.002$)

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Baba [78]	Large, consecutive, clinic-based cohort study (USA)	To determine gender differences in the PD phenotype	1.264 (67)	Age at onset: men 63 (11.1), women 63.8 (11)	Men 7.2 (6.4) Women 6.8 (6.4)	The proportion of individuals taking antiparkinsonian medications did not differ between gender (65% and 67% for men and women, respectively) LEDD was higher for men than women (618.9 ± 409.1 versus 526.8 ± 365.1 mg, $p < 0.01$) Women had more severe dyskinesia score than men (1.1 ± 2.4 versus 0.8 ± 2.1; $p < 0.05$)
Kompoliti [82]	Placebo-controlled, double-blind, parallel-design study	To compare the pharmacokinetics of levodopa and pramipexole (PPX) in men and women; to investigate gender effect of adjunct PPX treatment on levodopa pharmacokinetics	26 (46.1)	Men: 68.9 (5.1) Women: 69.3 (6.9)	NA	At baseline after levodopa administration (100 mg), women had a higher mean levodopa AUC_w (42.3 ± 7 mg versus 23.3 ± 7.3; $p = 0.0001$) and higher mean Cmax (1388 ± 42 mg versus 800 ± 33 mg; $p = 0.0019$) These sex differences for levodopa pharmacokinetics was sustained over low and high doses of PPX No differences in PPX pharmacokinetics between men and women
Kumagai [86]	Clinic-based cohort study (Japan)	To analyze sex differences in the levodopa pharmacokinetics in PD	128 (40.1)	77.9 (6.3)	3.2 (2.4)	The levodopa AUC and the AUC adjusted for body weight were found to be significantly greater in women compared with men ($p < 0.0001$ and $p < 0.0001$, respectively) In the elderly patients (>75 years old), the AUC and the AUC adjusted for body weight were significantly greater in women ($p < 0.0001$ and $p < 0.0001$, respectively)
Lubomski [80]	Cross-sectional study (3 centres in Australia)	To evaluate sex-related differences at onset in patients with PD	210 (61.4)	69.1 (10.8)	7.3 (5.7)	Women reported a significantly lower mean daily LEDD than men (750.7 ± 472.2 mg versus 898.1 ± 481.3 mg, $p = 0.03$) Levodopa requirement in man was significantly higher than in women and this trend persisted even after controlling for age, disease duration and severity ($p < 0.05$)
Lyons [135]	Retrospective study (USA)	To evaluate sex-related differences in PD patients	630 (50)	71.1 (7.6)	4.6 (4.6)	Women had higher MMSE and greater dyskinesia prevalence Men had higher UPDRS and were treated with greater LEDD
Nyholm [81]	Nationwide pharmaco-epidemiological survey (using data from "prescribed drug register", Sweden)	To investigate differences in the use and requirement of levodopa in PD To study the characteristics of low-dose and high-dose patients with PD	33.534 (46.5) (with at least one purchase of levodopa)	High dose group (≥ 1200 mg): 67.7 (NA) Low-dose group (≤ 400 mg): 70.5 (NA)	NA	The median daily dose was 465 mg for men and 395 mg for women ($p < 0.0001$) Significantly, more men were treated with doses >1200 mg daily There was a predominance of men in the high levodopa dose groups, administered both per os (69% versus 57%; p: ns) and infusion (77 versus 56%; p: ns)

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Martinelli [87]	Clinic-based cohort study (Italy)	To examine the potential sex-related differences in levodopa pharmacokinetics and their relation with the presence of dyskinesias	115 (58.3)	Men: 61 (11) Women: 59 (9)	Men: 6.2 (4.9) Women: 6.4 (4.0)	The area under the levodopa plasma concentration time curve, corrected for the LD test dose (AUCw) was higher in woman than in men ($p < 0.003$) and clearance values was reduced in women ($p < 0.003$) Dyskinesias were present in 38 patients (33%) but no sex-related differences were observed
Martinez-Ramirez [88]	Retrospective study (USA)	To formulate a definition and describe the clinical characteristics of PD patients with a ''brittle response'' (BR) to medications versus a ''non-brittle response'' (NBR), and characterize the use of deep brain stimulation (DBS) for this population	345 (25.2)	BR: 63.4 (12.4) NBR: 68.1 (10.2)	BR: 12.6 (7.5) NBR: 8.9 (5.2)	19/400 (5.5%) met criteria for BR PD The BR group included 58% females, compared to 29% in the NBR group ($P = 0.008$) BR group were younger ($p = 0.06$), had lower mean weight (63.5 vs. 79.6, $p = 0.001$), longer mean disease duration ($p = 0.003$), and had been on levodopa for more years compared to NBR patients (9.8 vs. 5.9, $p = 0.001$) UPDRS motor scores were higher (40.4 vs. 30.0, $p = 0.001$) in BR patients 63% of the BR group had undergone DBS surgery compared to 18% ($p = 0.001$). There was an overall positive benefit from DBS
Sharma [82]	Clinic- based cohort study	To evaluate risk factors for dyskinesia	220	Dyskinetic patients: 75 (8) Non-dyskinetic patients: 73 (8)	Dyskinetic patients: 8.6 (4) Non-dyskinetic patients: 5.3 (3.5)	Dyskinetic patients received higher daily dose of levodopa Dyskinetic patients had lost weight during the course of the disease (from 72 ± 15 to 66 ± 17 kg; $p = 0.002$) Dyskinetic patients received higher daily dose of levodopa per kilogram of body weight (8.4 ± 3.5 mg/kg vs. 6.0 ± 3.9 mg; $p = 0.003$) Weight-losers PD patients developed significantly more dyskinesia than non-weight-losers ($p = 0.002$) Weight-losers PD patients developed more dyskinesia than non-weight-losers ($p = 0.002$) Weight loss and daily levodopa dose per kilogram of body weight were the only significant predictors for dyskinesia in addition to disease duration
Sharma [83]	Pooled data from 056-Study (randomized, double blind study) and REAL-PET Study (randomized, double blind study)	To evaluate the relationship between levodopa dose per kilogram body weight and dyskinesia in PD	263 (65)	Men: 62 (9) Women: 62 (8)	Men: 23 (20) Women: 26 (31)	Men had higher body weight than women (78.6 ± 11 versus 65.9 ± 11 kg, $p < 0.001$), received higher levodopa dose (640 ± 388 mg versus 429 ± 278 mg, $p < 0.001$) and levodopa dose per kilogram body weight (8.3 ± 5 mg versus 6.6 ± 4 mg, $p < 0.01$) Dyskinetic patients received higher levodopa dose (respectively p 0.01 and p 0.003) and dose per kilogram body weight (respectively $p = 0.006$ and $p < 0.01$) Levodopa dose per kilogram body weight and younger age were the most important predictor for dyskinesia

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Umeh [77]	NINDS NET-PD Term Study-1 Randomized, multicenter, double blind study (45 sites in the US and Canada)	To evaluate the possible sex differences in the type of dopaminergic medication used and LEDD in early PD	1.741 (64.5)	61.8 (NA)	<5	There were not statistically differences in the proportions of type of dopaminergic medication between men and women with early PD A small but statistically significant difference was observed in the median unadjusted LEDD at baseline between women (300 mg) and men (325 mg), but this was not observed after controlling for disease duration, disease severity, and body weight F:M (%) treatment ratios: Levodopa alone 28%:29.6%; dopamine agonist alone 27%; 26.4%; Levodopa plus dopamine-agonist 19.3%: 17.9% respectively
Differences in management: surgical treatment						
Accolla [99]	Retrospective cohort study (Italy)	To investigate gender differences in surgery for PD	38 (57.8)	Women: 60.1 (8.5) Men: 59.7 (7)	Women: 13.5 (3.4) Men: 14.7 (5.8)	Before surgery, women had more dyskinesia than men After surgery, bradykinesia responded less but activities of daily living improved more in women
Willis [92]	Retrospective cohort study (USA)	To identify sociodemographic, clinical, and physician/practice factors associated with DBS	>650.000 Medicare beneficiaries	NA	NA	Black (AOR: 0.20, 95% CI 0.16–0.25) and Asian (AOR: 0.55, 95% CI 0.44–0.70) were considerably less likely to receive DBS than white patients Women (AOR: 0.79, 95% CI 0.75–0.83) also had lower odds of receiving DBS compared with men Beneficiaries treated in minority-serving PD practices were less likely to receive DBS, regardless of individual race (AOR: 0.76, 95% CI 0.66–0.87)
Chan [91]	Retrospective cohort study (USA)	To examine DBS use in PD to determine which factors, among a variety of demographic, clinical, and socioeconomic variables, drive DBS use in the United States	2.408.302 PD discharges from 2002 to 2009 of whom 18.312 of these discharges were for DBS	PD: 77.53 (13.19) PD with DBS: 63.66 (11.30) African American with PD: 75.86 (13.5)	NA	Younger age, male sex, increasing income quartile of patient zip code, large hospitals, teaching hospitals, urban setting, hospitals with higher number of annual discharges for PD, and increased countywide density of neurologists ($P < 0.05$) predicted use of DBS in PD Predictors of nonuse included African American race ($p < 0.001$), Medicaid use ($p < 0.001$), and increasing comorbidity score ($p < 0.001$)
Chandran [96]	Clinic-based cohort study (India)	To investigate gender differences in surgery for PD	51 (62.7)	Women: 54.5 (10.7) Men: 55.8 (10.7)	Women: 10.1 (4.6) Men: 11.1 (5.8)	Women presented lower doses of drugs ($p = 0.03$), worse emotional scores in PDQL ($p = 0.01$) and worse depression ($p = 0.03$) before surgery There was no gender difference in the surgical outcome, except a lesser reduction of dopaminergic drugs in women
Chiou [98]	Retrospective study (Taiwan)	To investigate gender-related factor in DBS for PD	72 (66.6)	61.1 (2.3)	7.9 (0.9)	Before surgery there women presented worse cognition and better response to levodopa There was no gender difference in the surgical outcome

Table 1 continued

Study	Type of study (country)	Aim(s) of the study	No. of PD patients (Men,%)	Age of PD patients,* years	Disease duration, * years	Main findings
Hamberg [94]	Clinic-based cohort interview (Sweden)	To investigate the decision-making process to undergo DBS from the patient's perspective, and explore any gender patterns in the participants' decision-making	39 (74)	64.1 (8.2)	NA	Three different approaches to DBS were identified among the patients: (1) 'Taking own initiative', included 48% of the patients and implied that the patients' own initiatives and arguments had been crucial for having surgery; (2) 'Agreeing when offered', and accepting DBS when suggested by doctors embraced 43%; (3) 'Hesitating and waiting' included <10% of the patients Most of the men were either 'taking own initiative' or 'agreeing when offered'. The 11 women were evenly distributed in all three approaches Among the interviewed, more women than men expressed strong fear of complications and more women consulted friends and relatives prior to deciding about DBS At time for surgery ten men but no woman were professionally active
Hariz [95]	Clinic-based cohort study (Sweden)	To investigate gender differences in surgery for PD	46 (63)	Women: 65.8 (8.1) Men: 65.7 (9.0)	Women: 15.1 (5.8) Men: 10.2 (5.6)	At surgery, women had a significantly longer duration of disease than men, higher Hoehn and Yahr scale and worse scores on UPDRS parts II–IV Following surgery, both men and women showed improvement, but women experienced greater benefit than men in activities of daily living, in emotions, and in social life
Hariz [97]	Clinic-based cohort study (Sweden)	To investigate gender differences in surgery for PD	49 (63.2)	Women: 57.6 (6.6) Men: 57.7 (7.8)	Women: 12.1 (5.3) Men: 12.7 (6.2)	At surgery, women had lower doses of medications, experienced more disability due to dyskinesia and mobility Following surgery, both men and women showed improvement, but women experienced greater benefit than men in activities of daily living and quality of life
Romito [100]	Clinic-based cohort (Italy)	To investigate gender differences in DBS for PD	20 (55)	56.4 (6.9)	14.3 (6.2)	Before surgery, there were no gender differences After surgery, there was a higher motor response after 1-year, but not after 3- and 5-year follow up in men Women had more persistent adverse events compared to men
Scelzo [101]	Clinic-based cohort (Multicentric, International)	To describe risk and management of pregnancy and delivery during treatment with DBS	11 women, of whom 3 with PD	NA	NA	With the exception of one abortion, all pregnancies and deliveries were uneventful

* Data are expressed in mean (standard deviation)

AOR, adjusted odds ratio; AUC, area under the curve; BR, brittle response; CI, confidence interval; DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DBS, deep brain stimulation; DSM-IV, diagnostic and statistical manual of the American Psychiatric Association—Fourth Edition; F, female; H&Y, Hoehn&Yahr stage; HC, healthy controls; HR, Hazard ratio; LEDD, levodopa equivalent daily dose; LID, levodopa-induced dyskinesia; M, male; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment battery; NA, not applicable; NBR, non-brittle response; NMS, non motor symptoms; NMSS, Non-Motor Symptoms Scale; OR, Odds Ratio; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PIGD, postural instability and gait disorders; PPX, pramipexole; PROPARK, PROfiling PARKinson's disease; PPMI, Parkinson's Progression Markers Initiative; RBD, REM behavior disorder; RR, relative risk; SCOPA-AUT, Sclae for Outcome in Parkinson Disease –Autonomic; SCOPA-COG, Scale for Outcome of Parkinson Disease-Cognition; UPDRS, Unified Parkinson's disease rating scale; UPSIT, University of Pennsylvania Smell Identification test, WOQ-19, the 19-item Wearing off Questionnaire

to the estrogens status [13, 14]. Indeed, gender differences in PD presentation may be attributable to biological factors; however, health-care seeking behavior should not be overlooked [15]. A study evaluating tertiary care referral in PD showed that the expected duration from onset to the movement disorders specialist visit for women was 61% greater than for men ($p = 0.003$) [16]. The effect of gender remained significant when adjusting the model for disease severity and historical features (age of onset and family PD history) and supported a referral delay in women irrespective of disease features [16].

Yet, once the disease has started, evidence reports shorter time to develop wearing off and dyskinesia in women than in men, arguing against the theory of the protective effect of estrogens [17–19]. According to a cross-sectional study enrolling 617 PD patients, the prevalence of wearing off was higher in women (72.5% versus 64%, $p = 0.034$) with female gender conferring an increased risk for wearing off equal to 80.1% [19]. Confirming previous findings [20], a prospective, population-based study on 189 de novo, PD patients showed that gender is the most important independent predictor of levodopa-induced dyskinesia, with an almost threefold increased risk in women compared to men, irrespective of body weight [18, 21]. As a matter of fact, along with younger age of onset, female gender has been associated with a shorter time to occurrence of levodopa-induced dyskinesia (Hazard Ratio = 1.82; 95% CI 1.14–2.89, $p = 0.011$) with a median time to dyskinesia of 4 years in women and 6 years in men [22].

Yet, the role of gender in determining either a more benign or aggressive motor disease course is far to be clear.

Non-motor symptoms

Although methodological issues (as the use of different scales) limit the comparison of the available data, the majority of studies suggest the existence of gender-related differences in non-motor symptoms (NMS) prevalence in PD. As a matter of fact, several studies showed that feelings of nervousness and sadness, constipation, restless legs and pain are more common in women, while daytime sleepiness, dribbling saliva, reduced interest in sex and problems having sex are more prevalent in men [23–27]. Indeed, since it is known that dopaminergic treatment may affect several NMS differently [28], as a major limitation these studies only included patients on dopaminergic treatment. By administering the Non-Motor Symptoms Questionnaire to 200 early, drug-native PD patients and 93 age- and sex-matched healthy controls, we were able to show PD-specific gender differences in NMS, irrespective of disease progression and dopaminergic therapy [29]. Our study showed that men with PD complained more frequently about dribbling, sadness/blues, loss of interest, anxiety, acting during dreams, and taste/smelling difficulties compared to healthy control men, while female PD patients reported more frequently loss of interest and anxiety compared to healthy control women [29]. In contrast with previous data on treated PD patients [23, 24, 30], female PD patients did not present higher prevalence of mood symptoms compared to male PD patients. Comparison with healthy controls showed that several NMS classically present in the promotor phase and pointing to subjects with subsequent development of PD in large population studies (i.e., sadness/blues, acting out during dreams, taste/smelling difficulties) [31–33] are more frequent in male than in female patients [29]. Further supporting the importance of these findings, Liu et al. described a combination of NMS that can best differentiate PD from controls [34]. Remarkably, in both men and women, poor olfaction was the most powerful NMS predicting PD diagnosis, followed by the Montreal Cognitive Assessment battery score, but, once again, gender made a difference, since dysautonomia was a predictor of PD diagnosis only in men, while REM sleep behavior disorder only in women [34]. The large sample size and the use of multiple detailed NMS assessment tools further corroborate the importance of these findings [34] (Table 1).

Yet, the role of gender in the response of NMS to dopamine replacement therapy was not established. Subsequently, we conducted a 2-year prospective assessment of gender-related differences in the burden of NMS before and after starting dopaminergic therapy showing that sadness/blues presented a significant percentage reduction compared to baseline in both sexes, while urgency, daytime sleepiness, weight gain and increase in sex drive presented a significant percentage increase only in men possibly in relation to both disease progression and dopaminergic treatment [35]. Confirming previous findings [27, 36], male gender was a risk factor for developing both dribbling (odds ratio = 10.29) and nocturia (odds ratio = 9.90), irrespective of therapy and clinical features [35].

However, as the disease progresses, NMS appear in the form of non-motor fluctuations more frequently in women than in men. By administering the 19-item Wearing off Questionnaire to 47 PD patients (M:F = 31:16) after 4 years since the start of dopaminergic treatment, we showed that mood-related non-motor fluctuations (i.e., anxiety, mood changes and pain) were more prevalent in women [37]. These findings possibly account for the higher prevalence of mood-related NMS reported by women in studies including PD patients on dopaminergic treatment and with different stages of disease [26, 27]. Strikingly, in our study no gender differences were detected in either dopaminergic or antidepressants/benzodiazepines intake, despite the higher frequency of non-motor fluctuations

evidenced in women, suggesting that non-motor fluctuations in women remain mostly underestimated and undertreated [37].

Regarding cognition, several studies suggest that, as opposite to the female prevalence of dementia (e.g., Alzheimer's disease) in the general population [4], male gender is a robust risk factor for development of cognitive impairment and dementia in PD [38–40]. Interestingly, recent data suggest that dementia prevalence in women with PD began to increase steadily after the age of 65 years, reaching male estimates only after 80 years of age [41]. Thus, mirroring the course of motor symptoms, PD NMS and cognitive disturbances start with a more benign phenotype in women compared to men, but then present a steadily progressive worsening as disease progresses. Indeed, NMS develop differently in women and men; taste and smell difficulties are reported mainly in men and anxiety in women, respectively, suggesting that the prodromal stage of PD proceeds differently in both sexes [42]. In turn, NMS may be useful to differentiate patients at PD risk if gender is included as an important variable. However, it has to be considered that pre-existing sex differences such as in olfaction might be further exacerbated by the onset of PD.

Biomarkers

Despite few data suggested gender differences for other biomarkers in PD [43–46], the most robust evidence is available for urate.

Previous prospective and case–control studies showed that lower urate concentrations predicted PD prognosis and were inversely associated with disease severity in men but not in women [47–50]. In a postmortem study, urate levels in cortical and striatal tissue were lower in PD than in controls in men only [51]. Intriguingly, more recent data further expand the relationship between urate and gender in PD. With a nested case–control study based on 90.214 participants of three ongoing US cohorts, Gao et al. obtained data for 388 new PD cases (52% men) and 1.267 matched healthy controls (35% men) [52]. Logistic regression analysis showed that men, but not women, with higher urate concentrations had a lower future risk of developing PD, suggesting that urate can be protective against PD risk or could slow disease progression during the preclinical stage of the disease in men only [52]. In addition, by performing a meta-analysis on urate and PD risk in men and women separately, the authors pooled their data with additional 325 incident PD cases and further confirmed this gender difference [52]. The pathophysiological explanations underlying such gender specificity of urate in determining PD risk remain speculative. Other factors might offset the potential neuroprotective effects of urate in women, or estrogens may predominate in determining the lower risk of PD among women [52]. On a practical ground, these data, combined with the evidence on NMS, further support the need for gender-based strategies involving clinical and serum biomarkers to identify prodromal PD cases [34].

Genetics

In this section, the available evidence on gender differences in genes determining PD susceptibility is examined, while the large body of pharmacogenetic data was left out of the scope of this review.

While variable evidence suggests that specific polymorphisms' expression may be influenced by gender [53-66), a number of studies support a role for LRRK2 status in either reverting or balancing the gender distribution in PD [67–71].

Mutations in the LRRK2 gene are among the most common genetic factors causing PD worldwide and particularly common in selected populations (e.g., Ashkenazi Jews and North African Berbers) [69]. LRRK2 mutations are inherited with an autosomal dominant pattern with incomplete and age-related penetrance. As a matter of fact, asymptomatic LRRK2 carriers represent the ideal setting to study prodromal PD [72]. Several studies suggest that PD LRRK2-associated PD patients are more likely women, as opposite to the gender distribution in glucocerebrosidase (GBA)-associated PD which mirrors the prevalence ratios in the general population [73]. Although a recent meta-analysis rebuts this finding and shows a 1:1 male to female ratio in LRRK2-associated PD [74], the factors associated with the possible rebalancing of the male to female ratio in LRRK2-associated PD compared to idiopathic PD are unknown. Indeed, there is a need for studies evaluating the effect of gender on both genetic and environmental factors determining the PD risk.

Gender differences in Parkinson's disease management

Pharmacological treatment

Although therapeutic recommendations for PD take into account age, motor disability as well as the presence of disease-related complications (i.e., motor fluctuations and neuropsychiatric complications), to date no gender-oriented advice is available [75, 76]. Yet, gender is one of the pivotal determinants of development of motor and non-motor fluctuations as well as dyskinesia (see above) [17–22, 37]. In addition, no ad hoc prospective studies have been conducted so far and the available evidence on the topic can be inferred from either retrospective studies or

the subanalysis of prospective data collected for different objectives.

As for the type of dopaminergic medication, evidence shows similar treatments assigned to men and women with PD, with no gender preference [77, 78]. As such, the NINDS NET-PD study, including data from 1.741 PD patients, reports similar gender ratios for treatment with levodopa alone, dopamine agonist alone or levodopa plus dopamine agonist [77]. Though, as for medication dosage, several studies demonstrate that men with PD are medicated with higher doses of either oral or infusional treatments, as evaluated with the levodopa equivalent daily dose (LEDD) [78–81]. However, when body weight is added as a covariate, the gender differences in LEDD recedes [77], suggesting the core of the matter might be the dosage adjustment according to the body weight [82, 83]. As opposite to dopamine agonists [84], several studies have demonstrated that levodopa pharmacokinetics is significantly affected by the body weight with an inverse correlation between the plasmatic levodopa concentration (i.e., the area under the curve, AUC) and body weight, which is lower in women on average. Arabia et al. observed a lower body weight (65.3 kg versus 73.9 kg, $p < 0.001$) with greater levodopa AUC in women with PD (6.45 μmol/l h among women versus 4.94 μmol/l h among men, $p = 0.002$) and reported an inverse correlation between AUC and $T_{1/2}$ (i.e., half-life) and body weight (respectively, $p < 0.001$ and $p = 0.001$) [85]. However, further evidence suggest that women present greater levodopa bioavailability with higher mean AUC (42.3 ± 7 mg versus 23.3 ± 7.3; $p < 0.0001$) and higher mean C_{max} (1388 ± 42 mg versus 800 ± 33 mg; $p < 0.001$) after administration of 100 mg of levodopa, irrespective of body weight [84, 86]. In addition, women display lower levodopa clearance levels, further justifying the greater levodopa bioavailability [87]. Recent evidence delineated the features characterizing a subgroup of patients reporting a "brittle response" to levodopa, defined as the presence of highly disabling dyskinesia after small doses (i.e., 100 mg or less per dose) [88]. Those extremely sensitive subjects are mainly women (58%) with lower body weight and body mass index (63.5 versus 79.6 kg, $p < 0.001$ and 22.3 versus 26.5, $p < 0.001$, respectively), longer disease duration and much many years on levodopa, but with lower dosage (12.6 versus 8.9 years, $p = 0.003$ and 9.8 versus 5.9 years, $p < 0.001$, respectively), compared to patients without a "brittle response" [88]. Although this study suggests new insight into the phenomenology of the response to levodopa, the genetic background of the patients with "brittle response" is overlooked [88].

Indeed, the lower female body weight alone cannot entirely account for the gender discrepancy in development of levodopa-related complication. PD is associated with a profound alteration in central control of energy metabolism determining continuous changes in body weight and composition and energy expenditure in relation to both disease progression and type of treatment [89]. Furthermore, genetic polymorphisms may also have a role in modulating the dyskinesia risk (e.g., DRD2 polymorphism has a protective effect against dyskinesia development only in men [20]). Intriguingly, not all PD patients convert to a "brittle response", suggesting this subgroup might have peculiar features placing them at risk for maladaptive plastic responses to levodopa [89]. There is a need for prospective ad hoc studies to clarify why women with PD have higher rates of levodopa-related complications and are at risk for presenting a "brittle response" to levodopa.

Surgical treatment

Several randomized clinical trials have shown bilateral subthalamic nucleus deep brain stimulation (DBS) to be effective in PD patients with motor fluctuations [90]. Notwithstanding, this option is underused in certain groups of patients, such as ethnic minorities and low-level socioeconomic status subjects [91, 92]. Strikingly, in spite of the higher risk of developing dyskinesia and motor fluctuations in women, female gender has been repetitively associated with lower utilization of DBS in PD [91–93]. The observation that in the western world the proportion of male patients who receive DBS exceeds the usual male/female predominance of PD might have several explanations as doctors' attitude and potential gender bias in proposing DBS, stronger fear for surgical risks among women or more initiative in men who autonomously demand for DBS [93, 94]. However, the lack of large ad hoc prospective studies prevents us from drawing conclusions on the reasons for the gender discrepancy in DBS access [92, 93]. As a matter of fact, women with PD perform DBS later than men displaying longer disease duration, more severe disease and much more dyskinesia at the time of surgery [95]. Yet, DBS provides benefit in both genders determining equal clinical improvement and reduction in medications with even greater impact on activities of daily living and quality of life in women [96–100]. Postponing DBS in PD women might have a detrimental impact on life planning. Recent reports demonstrate that, due to its efficacy on psychomotor status and treatment reduction, DBS is a safe option in the management of young PD women who wish to become pregnant [101]. However, there is the need to define strategies to prevent and control any worsening of clinical conditions during pregnancy and to consider device-related options (i.e., rechargeable battery to avoid battery replacement and subclavicular placement instead of abdominal) in women who plan to become pregnant [100].

Finally, DBS is a valid approach to relieve disability in patients with "brittle response" to levodopa (see above), who are mostly women [88].

The role of estrogens

Estrogens are likely contributors to gender differences in PD [102–104]. Although conflicting data are available, evidence would suggest a link between longer estrogen exposure during lifetime and both the decreased PD risk and milder features at onset in women [105–119]. Most women develop PD after menopause, further suggesting estrogen withdrawal has a role in disease pathogenesis [9, 13, 14]. Accordingly, preclinical evidence shows that estrogens are protective against dopaminergic damage. Animal models with estrogens deprivation show dopaminergic neuron loss, altered dopaminergic metabolism and transporter uptake, which can be partially reversed by the administration of exogenous estrogens [102–104].

A large body of evidence shows that estradiol and related compounds exert neuromodulatory and neuroprotective activities in the striatum and substantia nigra through several intracellular mechanisms that ultimately decrease apoptosis of neurons. In addition to these signal cascade effects, estrogens might impact PD pathogenesis via their influence on mitochondrial function and response to oxidative stress. Evidence demonstrates that estrogens might also prevent Lewy body deposition through specific alpha-synuclein anti-aggregation and fibril destabilization properties [102–104].

However, in contrast with the large body of preclinical evidence [104], a spoonful of studies on humans are available on the clinical effects of estrogens in PD. A small pilot study showed that estrogen replacement therapy in non-parkinsonian women increases putaminal dopamine active transporter as measured with TRODAT SPECT scan [120]. Although small trials have demonstrated mild efficacy of low-dose estrogens in improving motor disability and motor fluctuations in post-menopausal women [121–125], estrogens have not been further tested in larger cohort. Although there is an increasing interest of the research community in testing the disease-modifying effect of estrogens in different neurological conditions [126], clinical trials of estrogen face unique challenges possibly explaining the lack of data in larger PD cohort [123]. Estrogen is an endogenous compound with levels that naturally fluctuate throughout the lifecycle. Estrogen's effects are widespread in and outside the brain and

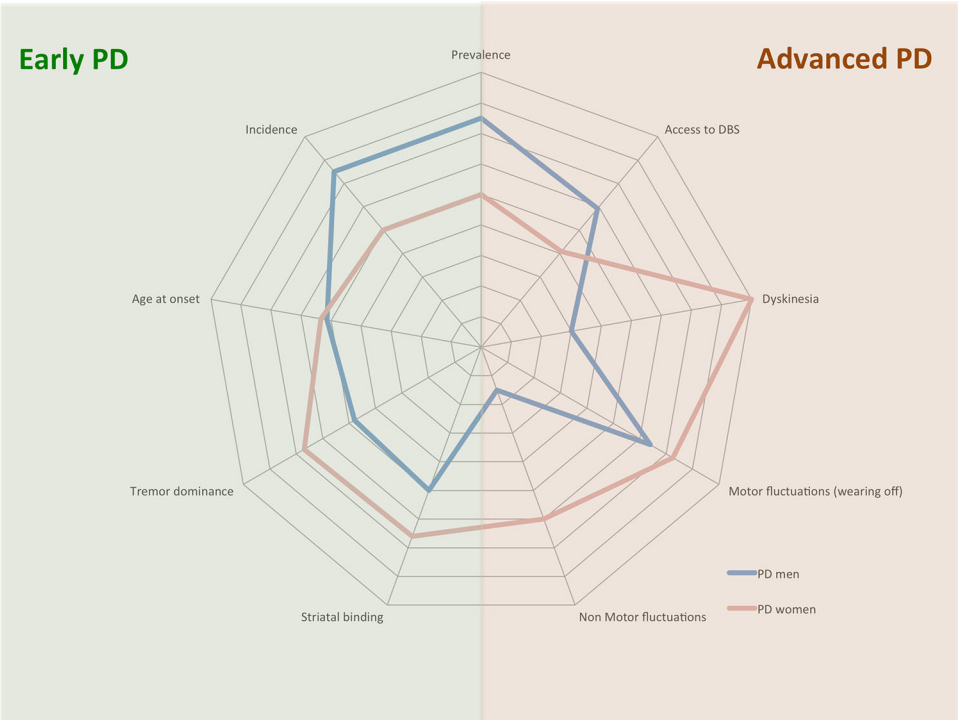

Fig. 1 Synoptic diagram showing gender difference in early (*left side*) and advanced (*right side*) PD. As for early PD, women have lower prevalence and incidence, slightly higher age at onset, higher tremor dominance and striatal uptake compared to men, justifying the definition of "more benign phenotype". As for advanced PD, women have more motor and non-motor fluctuations as well as dyskinesia and reduced access to DBS, thus challenging the definition of "more benign phenotype". *DBS* deep brain stimulation, *PD* Parkinson's disease

conventional study designs have difficulty assessing complex variables including variability in endogenous/exogenous estrogen exposure, and the interface between hormonal changes and the onset/progression of a chronic disease. Ultimately, as chronic estrogen exposure is associated with increased risk of breast cancer and coronary heart disease, risks may exceed benefits [127].

Conclusions

Here, we gathered evidence demonstrating the existence of gender differences in PD clinical phenotype, biomarkers and therapeutic management. Still, much work needs to be done to better understand the interaction between gender and genetics in determining the PD risk and clinical features. Several data demonstrate that PD in women starts with a more benign phenotype, likely due to the effect of estrogens. However, as the disease progresses, women are at higher risk of developing highly disabling treatment-related complications, such as motor and non-motor fluctuations as well as dyskinesia, compared with men. In addition, women have lower chances of receiving effective treatment for PD as DBS (Fig. 1). Taken together these findings challenge the definition of a more benign phenotype in women.

Improving our understanding in this field may result in implementation of strategies to identify prodromal PD cases and speed efforts to discern new directions for PD tailored treatment and management. We just got the evidence that gender does matter in PD [128]. It matters in many ways we did not expect. It also matters in ways we have not envisaged yet [1].

Acknowledgements This review was designed after the authors have been involved in a talk about "Gender differences in movement disorders" during the last meeting of the Italian LIMPE-DISMOV Academy held in Bari on May 4–6, 2016.

Compliance with ethical standards

Conflicts of interest The authors declare no financial disclosures related to the content of this article. The authors declare no conflict of interest.

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