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Association of women-specific health factors in the severity of Parkinson's disease

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Parkinson's disease (PD) is an age-related neurological disorder known for the observational differences in its risk, progression, and severity between men and women. While estrogen has been considered to be a protective factor in the development of PD, there is little known about the role that fluctuations in hormones and immune responses from sex-specific health experiences have in the disease's development and severity. We sought to identify women-specific health experiences associated with PD severity, after adjusting for known PD factors, by developing and distributing a women-specific questionnaire across the United States and creating multivariable models for PD severity. We created a questionnaire that addresses women's specific experiences and their PD clinical history and deployed it through The Parkinson's Foundation: PD Generation. To determine the association between women-specific health factors and PD severity, we constructed multivariable logistic regression models based on the MDS-UPDRS scale and the participants' questionnaire responses, genetics, and clinical data. For our initial launch in November 2021, we had 304 complete responses from PD GENEration. Univariate and multivariate logistic modeling found significant associations between major depressive disorder, perinatal depression, natural childbirth, *LRRK2* genotype, B12 deficiency, total hysterectomy, and increased PD severity. This study is a nationally available questionnaire for women's health and PD. It shifts the paradigm in understanding PD etiology and acknowledging how sex-specific experiences may contribute to PD severity. In addition, the work in this study sets the foundation for future research to investigate the factors behind sex differences in PD.

INTRODUCTION

As the average age of the global population increases, neurodegenerative diseases, like Parkinson's disease (PD), are a rising cause of concern because of the consequential global economic and societal burdens. With a drastically increased prevalence in the past two decades, PD is one of the fastest-growing neurological diseases worldwide, affecting ~1–3% of the population over 60 years old[1,2].

PD research has made substantial progress in deciphering what factors influence the disease's risk, progression, and severity. Genetics, environmental factors, and clinical history all contribute to the etiology of PD. Therefore, each person with PD may be the result of a unique combination of a different set of factors, hence the diverse spectrum of symptoms observed[3]. This might be one of the reasons why treatments have not been successful across the entire PD population.

To make this even more complicated, there is one important factor in PD etiology, biological sex, which has been understudied[4]. Estrogen is believed to be a protective factor against PD and perhaps one of the reasons why men are about 1.5 times more likely to have PD than women[5,6]. Aside from risk, PD varies in presentation, severity, and treatment success between sexes[7,8]. For example, women with PD have increased mortality compared to men with PD[9]. Furthermore, one study found that men and women with PD have different rates of progression and severity when adjusted for demographic variables[10]. Regarding PD severity in motor symptoms, two studies showed that there was poorer postural stability in women and greater rigidity in men[11,12]. For the severity of non-motor symptoms, women reported a higher severity of fatigue and mood-related symptoms[13,14]. A few studies also relayed that women with PD tended to have greater severity of depression and impairment in activities of daily living[11,12]. Thus, while previous studies have described potential sex differences in the epidemiology and clinical presentation of PD between men and women, the role that sex-specific factors, and particularly Women-specific health factors (WSHFs), may play in the differences observed is still poorly understood. These WSHFs encompass the sexual and reproductive health experiences that revolve around changes in hormonal and immunological changes (i.e., menses, hormone-related medications, family planning, surgeries, and menopause) and have been overlooked in both research and clinical discussions[15,16].

In fact, only a few studies have examined the association between the disease and certain individual WSHFs, such as menses, contraceptives, surgeries, hormonal disorders, pregnancies, hormone-replacement therapy, and menopause. Moreover, the results have been highly contradictory[5,17–19], in part due to the lack of attention toward these sex-specific factors, as well as the neglect of gathering the necessary data.

Beyond the lack of representation of women's health in research, WSHFs are often ignored or excluded in clinical trials in and outside the PD field. One study found that ~42% of clinical trial protocols required contraception or sterility for women without providing any explanation, making women have a lower chance of being included in a clinical trial and resulting in a decreased representation of WSHFs in clinical research. Without

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incorporating these WSHFs, the scientific community ignores the basic biology of women and continues to inaccurately represent the clinical manifestations and treatment outcomes for 50% of the population[20].

This exploratory study seeks to shed light upon the role WSHFs play in the severity of PD in women by deploying a national questionnaire and analyzing the responses together with the participants' genetic and clinical histories. Our study not only includes WSHFs as equally weighted variables amongst known variables in PD severity but also allows for the data to be collected in a comprehensive way through the questionnaire.

We hypothesized that certain WSHFs would be associated with greater PD severity even after adjusting for non-specific-sex factors. This study sets the stage for acknowledging sex-specific experiences in an age-related neurological disorder.

RESULTS

PD GENEration population
The questionnaire was sent to 966 women with PD enrolled with the Parkinson's Foundation PD GENEration. Of the returned surveys, 304 women gave complete responses, providing a response rate of 31.5%. Overall, respondents averaged 64.7 years in age (±9.1), with a mean age at diagnosis of 58.5 years (±10.4). Women completing the survey had an average of 6.2 years of disease duration (±5.3) since they were diagnosed with PD (Table 1). Since PD GENEration tests participants for seven known PD genes, we are able to see the genetic status of each respondent. Within our cohort, we have women with GBA (10%), LRRK2 (8%), PINK1 (1%), PRKN (4%), and VPS35 (1.3%) mutations[21,22]. The entirety of demographic information collected for every PD GENEration respondent by severity group can be found in Table 1.

As our previous work stated, the women's questionnaire is composed of questions that are specific to a woman's reproductive lifecycle. Participants in this cohort have a mean MoCA score of 27.4 (±2.3) (data not shown), indicating the women who completed this questionnaire had high cognitive aptitude and were able to complete the questionnaire without issues with impairment. Most respondents experienced their onset of PD during menopause (i.e., at least 1 year after their last menstrual cycle) (73.7%), compared to those that either experienced PD symptoms during perimenopause (8.8%) or during regular menses (17.5%). When asked about pregnancy-related experiences, the majority of respondents have had children (74.3%), although we noticed a higher incidence of infertility experiences (32.2%) or perinatal complications (31.2%) compared to non-PD women. It is important to note that within the United States, the national prevalence rate of history of primary and secondary infertility among women ranges from 15.5 to 19%[23,24]. A summary of all responses from the women's questionnaire can be found in Table 2.

Univariate modeling
Variables were extracted from the questionnaire (WSHFs) and PD GENEration database. Thus, we were able to include other non-sex-specific factors for PD and comorbidity history in our modeling. From our univariate models, we found that certain factors, such as PD medications, depression, loss of smell, PTSD, B12 deficiency, peripheral neuropathy, and flair-up migraines, were associated with a moderate/severe UPDRS score within at least one of the UPDRS Parts in women. Interestingly, for women-specific health factors, we saw that medications feeling less effective during menses, tubal ligation, mastectomy, total hysterectomy, vaginal birth, gestational diabetes, peri- and postnatal depression, and perinatal bacterial infection were associated with a moderate/severe PD phenotype. A full summary

of the univariate logistic regression with the sample size, OR (95% CI), and p values can be seen in Supplementary Table 1.

Multivariable modeling
To further assess the role of WSHFs and PD severity, we constructed multivariable logistics regression models by using variables that were significant in the univariate models and adjusting for age, disease duration, and medication. From Part I, having depression as a current diagnosis was associated with a moderate/severe PD severity phenotype (OR = 9.22 (3.31, 25.71), $p < 0.001$). In terms of pregnancy-related experiences, we found that having a natural (vaginal) birth was significantly associated with the moderate/severe cohort (OR = 4.48 (1.10, 18.20), $p = 0.036$), and postpartum depression demonstrated an association that did not reach conventional statistical significance (OR = 4.17 (0.91, 19.20), $p = 0.067$). Through our modeling, we noticed that "other comorbidities" was significant as well (OR = 3.91 (1.51, 10.14), $p = 0.005$). This was gathered as part of PD GENEration's clinical history, where participants can include specific disorders they were diagnosed with; these comorbidities are listed in Supplementary Table 2. For Part II, we saw that years since diagnosis was significant (OR = 1.17 (1.09, 1.25), $p < 0.001$), which is expected as Part II assesses motor experiences in daily living. Depression and perinatal depression were significantly associated with the moderate/severe PD phenotype (OR = 2.33 (1.13, 4.80), $p = 0.022$ and OR = 6.72 (1.35, 33.43), $p = 0.020$, respectively). In Part III, the motor examination, having a LRRK2 mutation (OR = 6.74 (1.62, 28.00), $p = 0.009$), total hysterectomy (OR = 5.46 (1.74, 17.18), $p = 0.004$), and being diagnosed with B12 deficiency (OR = 6.22 (1.69, 22.95), $p = 0.006$) were significantly associated with higher PD severity. For Part IV, only years since diagnosis was significant (OR = 1.17 (1.06, 1.29), $p = 0.002$). Overall, the concordance statistic (c-statistic) for these four regression models demonstrated high accuracy for discerning PD severity for women within this cohort (Part I: 0.874, Part II: 0.805, Part III 0.791, and Part IV: 0.782). The univariate variables in the multivariable regressions with the c-statistic, OR (95% CI), and p values are summarized in Table 3.

DISCUSSION
This study is the first of its nature to look at WSHFs concerning PD severity in women within the U.S. through the deployment of a women-specific health questionnaire. We leveraged PD GENEration's unique dataset of clinical and genetic health data from PD participants, coupled with the questionnaire responses, to develop multivariable logistic models to assess if WSHFs contribute to PD severity after adjusting for other non-sex-specific factors. Using Goetz et al.'s thresholds, we created mild vs. moderate/severe groups for PD phenotype for each subpart of the UPDRS assessment. Our analysis found that WSHFs, such as perinatal depression, delivery of children through vaginal birth, and history of a total hysterectomy, were associated with a severe PD phenotype, suggesting that WSHFs are important variables to be considered for PD severity in women. Aside from WSHFs, non-sex-specific factors, like major depression disorder, LRRK2 mutation carrier status, and B12 deficiency, were seen amongst women with a more severe phenotype compared to those with a mild PD phenotype. This study sets the stage for acknowledging the role of WSHFs in the severity of PD. While there have been studies looking at PD risk and some WSHFs, they overlook the growing population of women who have already been diagnosed with PD and thus have a declining health-related quality of life[5,17–19,25–33].

Through our multivariable logistic regression models, we found that certain non-sex-specific and sex-specific factors were associated with a moderate/severe PD phenotype within each subpart of the UPDRS assessment. One such non-sex-specific

Table 1. Characteristics of the study sample stratified by UPDRS parts I-IV (A-D) severity groups.

	Total	Mild	Moderate/Severe	p value
A. Characteristics of the study sample: stratified by part I severity groups				
Sample size	160	112	48	
Age, mean (sd)	64.4 (9.2)	64.1 (9.2)	65.0 (9.2)	0.60[a1]
Age at diagnosis, mean (sd)	58.2 (10.3)	58.6 (9.9)	57.3 (11.3)	0.45[a1]
Years since symptom onset, mean (sd)	8.6 (6.1)	7.9 (5.7)	10.4 (6.7)	**0.017[a1]**
Years since diagnosis, mean (sd)	6.1 (5.3)	5.5 (4.7)	7.7 (6.2)	**0.032[a2]**
Ethnicity, n (%)				0.55[d]
Hispanic/Latino	3 (1.9)	3 (2.7)	0 (0.00)	
Not Hispanic or Latino	157 (98.1)	109 (97.3)	48 (100.0)	
Race, n (%)				0.89[d]
Asian	1 (0.63)	1 (0.89)	0 (0.00)	
Asian, Native Hawaiian or Other Pacific Islander	1 (0.63)	1 (0.89)	0 (0.00)	
Asian, White	1 (0.63)	1 (0.89)	0 (0.00)	
Black or African American	1 (0.63)	1 (0.89)	0 (0.00)	
Black or African American, White	1 (0.63)	0 (0.00)	1 (2.1)	
White	154 (96.3)	107 (95.5)	47 (97.9)	
White, Native American	1 (0.63)	1 (0.89)	0 (0.00)	
Genetic status, n (%)[e]				0.37[d]
GBA	17 (10.8)	13 (11.8)	4 (8.3)	
LRRK2	13 (8.2)	8 (7.3)	5 (10.4)	
PINK1	1 (0.63)	1 (0.91)	0 (0.00)	
PRKN	6 (3.8)	2 (1.8)	4 (8.3)	
VPS35	1 (0.63)	1 (0.91)	0 (0.00)	
None	120 (75.9)	85 (77.3)	35 (72.9)	
Medications, n (%) [e]				
Levodopa	116 (72.5)	78 (69.6)	38 (79.2)	0.22[c]
Entacapone	3 (1.9)	0 (0.00)	3 (6.3)	**0.026[d]**
Carbidopa, Levodopa, and Entacapone (Stalevo)	12 (7.6)	6 (5.4)	6 (12.8)	0.18[d]
Tolcapone (excluding Stalevo)	0 (0.00)	0 (0.00)	0 (0.00)	
Apomorphine (injection, infusion, other)	0 (0.00)	0 (0.00)	0 (0.00)	
Pramipexole	22 (13.9)	14 (12.6)	8 (17.0)	0.46[c]
Ropinirole	11 (7.0)	4 (3.6)	7 (14.9)	**0.017[d]**
Rotigotine	6 (3.8)	4 (3.6)	2 (4.3)	0.99[d]
Rasagiline	33 (20.9)	25 (22.5)	8 (17.0)	0.44[c]
Selegiline (oral, sublingual)	3 (1.9)	2 (1.8)	1 (2.1)	0.99[d]
Amantadine (liquid, infusion)	17 (10.8)	14 (12.6)	3 (6.4)	0.25[c]
Any_medication, n (%)	137 (85.6)	92 (82.1)	45 (93.8)	0.055[c]
Current comorbidities, n (%)				
ALS	0 (0.00)	0 (0.00)	0 (0.00)	
Alzheimer's disease	0 (0.00)	0 (0.00)	0 (0.00)	
Arrythmia/Atrial fibrillation	10 (6.3)	7 (6.3)	3 (6.3)	0.99[d]
Arthritis	85 (53.1)	54 (48.2)	31 (64.6)	0.057[c]
B12 deficiency	16 (10.0)	9 (8.0)	7 (14.6)	0.25[d]
Cancer	6 (3.8)	4 (3.6)	2 (4.2)	0.99[d]
Congestive heart failure	1 (0.63)	0 (0.00)	1 (2.1)	0.30[d]
Crohn's disease/ulcerative colitis	1 (0.63)	0 (0.00)	1 (2.1)	0.30[d]
Depression	44 (27.5)	18 (16.1)	26 (54.2)	**<0.001[c]**
Diabetes Mellitus (adult onset)	6 (3.8)	3 (2.7)	3 (6.3)	0.37[d]
Diabetes Mellitus (childhood onset)	1 (0.63)	1 (0.89)	0 (0.00)	0.99[d]
Gaucher disease	1 (0.63)	1 (0.89)	0 (0.00)	0.99[d]
Gout	2 (1.3)	2 (1.8)	0 (0.00)	0.99[d]
Hearing loss	39 (24.4)	23 (20.5)	16 (33.3)	0.084[c]
Hip fracture	0 (0.00)	0 (0.00)	0 (0.00)	
Hyper cholesterolemia (high cholesterol)	44 (27.5)	28 (25.0)	16 (33.3)	0.28[c]
Hypertension (high blood pressure)	30 (18.8)	22 (19.6)	8 (16.7)	0.66[c]
Liver	2 (1.3)	2 (1.8)	0 (0.00)	0.99[d]
Loss of smell	68 (42.5)	49 (43.8)	19 (39.6)	0.63[c]
Lung disease (including emphysema)	11 (6.9)	6 (5.4)	5 (10.4)	0.31[d]

Table 1 continued

	Total	Mild	Moderate/Severe	p value
Multiple sclerosis	0 (0.00)	0 (0.00)	0 (0.00)	
Myocardial infarction (heart attack)	0 (0.00)	0 (0.00)	0 (0.00)	
Normal pressure hydrocephalus	0 (0.00)	0 (0.00)	0 (0.00)	
Other	60 (37.5)	36 (32.1)	24 (50.0)	*0.033[c]*
Peptic ulcer disease	1 (0.63)	0 (0.00)	1 (2.1)	0.30[d]
Peripheral neuropathy	17 (10.6)	13 (11.6)	4 (8.3)	0.54[c]
Peripheral vascular disease	2 (1.3)	1 (0.89)	1 (2.1)	0.51[d]
PTSD	9 (5.6)	3 (2.7)	6 (12.5)	*0.022[d]*
Recreational drug use	9 (5.6)	6 (5.4)	3 (6.3)	0.99[d]
Renal insufficiency (kidney disease)	4 (2.5)	2 (1.8)	2 (4.2)	0.58[d]
Seizure, fit, convulsion or unexplained loss of consciousness	2 (1.3)	0 (0.00)	2 (4.2)	0.089[d]
Stroke, mini stroke, CVA (cerebrovascular accident) or TIA (transient ischemic attack)	2 (1.3)	0 (0.00)	2 (4.2)	0.089[d]
Thyroid disease (not cancer, including Grave's disease)	32 (20.0)	20 (17.9)	12 (25.0)	0.30[c]
UPDRS score				
Part 1, mean (sd)	8.5 (6.1)	5.3 (2.7)	16.0 (5.1)	*<0.001[a2]*
Part 2, mean (sd)	7.6 (6.7)	5.6 (4.6)	12.2 (8.3)	*<0.001[a2]*
Part 3, mean (sd)[e]	21.4 (12.0)	20.6 (10.8)	23.4 (14.2)	0.26[a2]
Part 4, mean (sd)[e]	3.0 (3.4)	2.5 (2.9)	4.1 (3.9)	*0.012[a2]*

B. Characteristics of the study sample: stratified by part II severity groups

	Total	Mild	Moderate/Severe	p value
Sample size	302	246	56	
Age, mean (sd)	64.7 (9.0)	64.4 (9.2)	65.7 (8.2)	0.34[a1]
Age at diagnosis, mean (sd)	58.4 (10.4)	59.3 (9.9)	54.8 (11.9)	*0.004[a1]*
Years since symptom onset, mean (sd)	8.8 (6.5)	7.6 (5.4)	14.0 (8.3)	*<0.001[a2]*
Years since diagnosis, mean (sd)	6.2 (5.3)	5.2 (3.8)	10.9 (7.8)	*<0.001[a2]*
Ethnicity, n (%)				0.99[d]
Hispanic/Latino	7 (2.3)	6 (2.4)	1 (1.8)	
Not Hispanic or Latino	293 (97.0)	238 (96.7)	55 (98.2)	
Unknown	2 (0.66)	2 (0.81)	0 (0.00)	
Race, n (%)				0.99[d]
Asian	2 (0.66)	2 (0.81)	0 (0.00)	
Asian, Native Hawaiian or Other Pacific Islander	1 (0.33)	1 (0.41)	0 (0.00)	
Asian, White	2 (0.66)	2 (0.81)	0 (0.00)	
Black or African American	3 (0.99)	3 (1.2)	0 (0.00)	
Black or African American, White	1 (0.33)	1 (0.41)	0 (0.00)	
Hispanic	2 (0.66)	2 (0.81)	0 (0.00)	
Middle Eastern	1 (0.33)	1 (0.41)	0 (0.00)	
Unknown or decline to state	3 (0.99)	3 (1.2)	0 (0.00)	
White	286 (94.7)	230 (93.5)	56 (100.0)	
White, Native American	1 (0.33)	1 (0.41)	0 (0.00)	
Genetic status, n (%)[f]				0.75[d]
GBA	30 (10.0)	23 (9.5)	7 (12.5)	
LRRK2	24 (8.0)	21 (8.6)	3 (5.4)	
PINK1	3 (1.00)	3 (1.2)	0 (0.00)	
PRKN	11 (3.7)	8 (3.3)	3 (5.4)	
VPS35	4 (1.3)	3 (1.2)	1 (1.8)	
None	227 (75.9)	185 (76.1)	42 (75.0)	
Medications, n (%)[f]				
Levodopa	220 (72.8)	173 (70.3)	47 (83.9)	*0.039[c]*
Entacapone	7 (2.3)	5 (2.0)	2 (3.6)	0.62[d]
Carbidopa, Levodopa, and Entacapone (Stalevo)	20 (6.7)	14 (5.8)	6 (10.7)	0.23[d]
Tolcapone (excluding Stalevo)	0 (0.00)	0 (0.00)	0 (0.00)	
Apomorphine (injection, infusion, other)	0 (0.00)	0 (0.00)	0 (0.00)	
Pramipexole	31 (10.4)	24 (9.9)	7 (12.5)	0.56[c]

Table 1 continued

Ropinirole	25 (8.4)	16 (6.6)	9 (16.1)	*0.030[d]*
Rotigotine	12 (4.0)	7 (2.9)	5 (8.9)	0.053[d]
Rasagiline	67 (22.4)	59 (24.3)	8 (14.3)	0.11[c]
Selegiline (oral, sublingual)	15 (5.0)	14 (5.7)	1 (1.8)	0.32[d]
Amantadine (liquid, infusion)	40 (13.4)	28 (11.5)	12 (21.4)	*0.050[c]*
Any_medication, *n* (%)	265 (87.7)	211 (85.8)	54 (96.4)	*0.028[c]*
Current comorbidities, *n* (%)				
ALS	0 (0.00)	0 (0.00)	0 (0.00)	
Alzheimer's disease	0 (0.00)	0 (0.00)	0 (0.00)	
Arrythmia/Atrial fibrillation	23 (7.6)	18 (7.3)	5 (8.9)	0.78[d]
Arthritis	153 (50.7)	124 (50.4)	29 (51.8)	0.85[c]
B12 deficiency	27 (8.9)	22 (8.9)	5 (8.9)	0.99[c]
Cancer	19 (6.3)	14 (5.7)	5 (8.9)	0.36[d]
Congestive heart failure	3 (0.99)	1 (0.41)	2 (3.6)	0.089[d]
Crohn's disease/ulcerative colitis	1 (0.33)	1 (0.41)	0 (0.00)	0.99[d]
Depression	82 (27.2)	56 (22.8)	26 (46.4)	*<0.001[c]*
Diabetes Mellitus (adult onset)	12 (4.0)	10 (4.1)	2 (3.6)	0.99[d]
Diabetes Mellitus (childhood onset)	1 (0.33)	1 (0.41)	0 (0.00)	0.99[d]
Gaucher disease	1 (0.33)	1 (0.41)	0 (0.00)	0.99[d]
Gout	4 (1.3)	4 (1.6)	0 (0.00)	0.99[d]
Hearing loss	79 (26.2)	59 (24.0)	20 (35.7)	0.071[c]
Hip fracture	0 (0.00)	0 (0.00)	0 (0.00)	
Hyper cholesterolemia (high cholesterol)	86 (28.5)	74 (30.1)	12 (21.4)	0.20[c]
Hypertension (high blood pressure)	70 (23.2)	55 (22.4)	15 (26.8)	0.48[c]
Liver	4 (1.3)	3 (1.2)	1 (1.8)	0.56[d]
Loss of smell	122 (40.4)	92 (37.4)	30 (53.6)	*0.026[c]*
Lung disease (including emphysema)	20 (6.6)	15 (6.1)	5 (8.9)	0.39[d]
Multiple sclerosis	1 (0.33)	1 (0.41)	0 (0.00)	0.99[d]
Myocardial infarction (heart attack)	0 (0.00)	0 (0.00)	0 (0.00)	
Normal pressure hydrocephalus	0 (0.00)	0 (0.00)	0 (0.00)	
Other	104 (34.4)	85 (34.6)	19 (33.9)	0.93[c]
Peptic ulcer disease	5 (1.7)	2 (0.81)	3 (5.4)	*0.046[d]*
Peripheral neuropathy	36 (11.9)	23 (9.3)	13 (23.2)	*0.004[c]*
Peripheral vascular disease	4 (1.3)	2 (0.81)	2 (3.6)	0.16[d]
PTSD	16 (5.3)	12 (4.9)	4 (7.1)	0.51[d]
Recreational drug use	15 (5.0)	13 (5.3)	2 (3.6)	0.99[d]
Renal insufficiency (kidney disease)	7 (2.3)	4 (1.6)	3 (5.4)	0.12[d]
Seizure, fit, convulsion or unexplained loss of consciousness	2 (0.66)	1 (0.41)	1 (1.8)	0.34[d]
Stroke, mini stroke, CVA (cerebrovascular accident) or TIA (transient ischemic attack)	4 (1.3)	2 (0.81)	2 (3.6)	0.16[d]
Thyroid disease (not cancer, including Grave's disease)	61 (20.2)	48 (19.5)	13 (23.2)	0.53[c]
UPDRS score				
Part 1, mean (sd)[f]	8.5 (6.1)	7.0 (4.4)	15.1 (7.6)	*<0.001[a2]*
Part 2, mean (sd)	7.5 (6.3)	5.1 (3.3)	18.1 (5.1)	*<0.001[a2]*
Part 3, mean (sd)[f]	21.4 (12.0)	19.7 (10.2)	29.3 (16.1)	*0.008[a2]*
Part 4, mean (sd)[f]	3.0 (3.4)	2.5 (3.0)	5.0 (4.1)	*0.005[a2]*
C. Characteristics of the study sample: stratified by part III severity groups				
Sample size	141	114	27	
Age, mean (sd)	64.1 (8.7)	64.0 (8.8)	64.6 (8.5)	0.72[a1]
Age at diagnosis, mean (sd)	57.9 (9.7)	58.1 (9.5)	56.9 (10.6)	0.55[a1]
Years since symptom onset, mean (sd)	8.8 (6.0)	8.5 (5.6)	10.1 (7.2)	0.19[a1]
Years since diagnosis, mean (sd)	6.2 (5.2)	5.9 (4.6)	7.8 (7.2)	0.19[a2]
Ethnicity, *n* (%)				0.99[d]
Hispanic/Latino	3 (2.1)	3 (2.6)	0 (0.00)	

Table 1 continued

Not Hispanic or Latino	138 (97.9)	111 (97.4)	27 (100.0)	
Race, n (%)				0.58[d]
Asian, Native Hawaiian or Other Pacific Islander	1 (0.71)	1 (0.88)	0 (0.00)	
Asian, White	1 (0.71)	0 (0.00)	1 (3.7)	
Black or African American, White	1 (0.71)	1 (0.88)	0 (0.00)	
White	137 (97.2)	111 (97.4)	26 (96.3)	
White, Native American	1 (0.71)	1 (0.88)	0 (0.00)	
Genetic status, n (%)[g]				0.096[d]
GBA	14 (10.1)	10 (8.9)	4 (14.8)	
LRRK2	11 (7.9)	6 (5.4)	5 (18.5)	
PINK1	1 (0.72)	1 (0.89)	0 (0.00)	
PRKN	6 (4.3)	4 (3.6)	2 (7.4)	
VPS35	1 (0.72)	1 (0.89)	0 (0.00)	
None	106 (76.3)	90 (80.4)	16 (59.3)	
Medications, n (%) [g]				
Levodopa	103 (73.0)	85 (74.6)	18 (66.7)	0.41[c]
Entacapone	3 (2.1)	2 (1.8)	1 (3.7)	0.48[d]
Carbidopa, Levodopa, and Entacapone (Stalevo)	10 (7.2)	8 (7.1)	2 (7.4)	0.99[d]
Tolcapone (excluding Stalevo)	0 (0.00)	0 (0.00)	0 (0.00)	
Apomorphine (injection, infusion, other)	0 (0.00)	0 (0.00)	0 (0.00)	
Pramipexole	19 (13.7)	14 (12.5)	5 (18.5)	0.53[d]
Ropinirole	10 (7.2)	9 (8.0)	1 (3.7)	0.69[d]
Rotigotine	5 (3.6)	2 (1.8)	3 (11.1)	0.050[d]
Rasagiline	29 (20.9)	24 (21.4)	5 (18.5)	0.74[c]
Selegiline (oral, sublingual)	3 (2.1)	3 (2.7)	0 (0.00)	0.99[d]
Amantadine (liquid, infusion)	14 (10.1)	10 (8.9)	4 (14.8)	0.47[d]
Any_medication, n (%)	121 (85.8)	99 (86.8)	22 (81.5)	0.54[d]
Current comorbidities, n (%)				
ALS	0 (0.00)	0 (0.00)	0 (0.00)	
Alzheimer's disease	0 (0.00)	0 (0.00)	0 (0.00)	
Arrythmia/Atrial fibrillation	9 (6.4)	8 (7.0)	1 (3.7)	0.99[d]
Arthritis	75 (53.2)	64 (56.1)	11 (40.7)	0.15[c]
B12 deficiency	15 (10.6)	8 (7.0)	7 (25.9)	**0.010[d]**
Cancer	5 (3.5)	4 (3.5)	1 (3.7)	0.99[d]
Congestive heart failure	1 (0.71)	0 (0.00)	1 (3.7)	0.19[d]
Crohn's disease/ulcerative colitis	1 (0.71)	1 (0.88)	0 (0.00)	0.99[d]
Depression	39 (27.7)	30 (26.3)	9 (33.3)	0.46[c]
Diabetes mellitus (adult onset)	6 (4.3)	4 (3.5)	2 (7.4)	0.32[d]
Diabetes mellitus (childhood onset)	0 (0.00)	0 (0.00)	0 (0.00)	
Gaucher disease	1 (0.71)	0 (0.00)	1 (3.7)	0.19[d]
Gout	2 (1.4)	2 (1.8)	0 (0.00)	0.99[d]
Hearing loss	35 (24.8)	29 (25.4)	6 (22.2)	0.73[c]
Hip fracture	0 (0.00)	0 (0.00)	0 (0.00)	
Hyper cholesterolemia (high cholesterol)	39 (27.7)	32 (28.1)	7 (25.9)	0.82[c]
Hypertension (high blood pressure)	27 (19.1)	21 (18.4)	6 (22.2)	0.65[c]
Liver	2 (1.4)	2 (1.8)	0 (0.00)	0.99[d]
Loss of smell	59 (41.8)	45 (39.5)	14 (51.9)	0.24[c]
Lung disease (including emphysema)	9 (6.4)	6 (5.3)	3 (11.1)	0.37[d]
Multiple sclerosis	0 (0.00)	0 (0.00)	0 (0.00)	
Myocardial Infarction (heart attack)	0 (0.00)	0 (0.00)	0 (0.00)	
Normal pressure hydrocephalus	0 (0.00)	0 (0.00)	0 (0.00)	
Other	53 (37.6)	47 (41.2)	6 (22.2)	0.067[c]
Peptic ulcer disease	1 (0.71)	0 (0.00)	1 (3.7)	0.19[d]
Peripheral neuropathy	13 (9.2)	11 (9.6)	2 (7.4)	0.99[d]

Table 1 continued

Peripheral vascular disease	2 (1.4)	0 (0.00)	2 (7.4)	**_0.036_**[d]
PTSD	8 (5.7)	5 (4.4)	3 (11.1)	0.18[d]
Recreational drug use	8 (5.7)	7 (6.1)	1 (3.7)	0.99[d]
Renal insufficiency (kidney disease)	3 (2.1)	3 (2.6)	0 (0.00)	0.99[d]
Seizure, fit, convulsion or unexplained loss of consciousness	1 (0.71)	1 (0.88)	0 (0.00)	0.99[d]
Stroke, mini stroke, CVA (cerebrovascular accident) or TIA (transient ischemic attack)	1 (0.71)	0 (0.00)	1 (3.7)	0.19[d]
Thyroid disease (not cancer, including Grave's disease)	28 (19.9)	24 (21.1)	4 (14.8)	0.47[c]
UPDRS score				
Part 1, mean (sd)	8.2 (5.7)	8.0 (5.4)	9.0 (6.7)	0.42[a1]
Part 2, mean (sd)	7.1 (6.1)	6.4 (5.5)	10.3 (7.2)	**_0.002_**[a1]
Part 3, mean (sd)	21.4 (12.0)	17.1 (7.6)	39.8 (9.0)	**_<0.001_**[a1]
Part 4, mean (sd)[g]	3.0 (3.4)	2.7 (3.2)	3.9 (4.1)	0.14[a1]

D. Characteristics of the study sample: stratified by part IV severity groups

Sample size	139	96	43	
Age, mean (sd)	64.5 (8.9)	64.3 (9.8)	65.0 (6.7)	0.59[a2]
Age at diagnosis, mean (sd)	58.0 (10.0)	59.2 (9.9)	55.4 (10.0)	**_0.039_**[a1]
Years since symptom onset, mean (sd)	8.9 (6.1)	7.5 (5.1)	12.1 (7.1)	**_<0.001_**[a2]
Years since diagnosis, mean (sd)	6.5 (5.3)	5.1 (3.9)	9.6 (6.4)	**_<0.001_**[a2]
Ethnicity, _n_ (%)				0.55[d]
Hispanic/Latino	3 (2.2)	3 (3.1)	0 (0.00)	
Not Hispanic or Latino	136 (97.8)	93 (96.9)	43 (100.0)	
Race, _n_ (%)				0.90[d]
Asian	1 (0.72)	1 (1.04)	0 (0.00)	
Asian, Native Hawaiian or Other Pacific Islander	1 (0.72)	1 (1.04)	0 (0.00)	
Asian, White	1 (0.72)	1 (1.04)	0 (0.00)	
Black or African American	1 (0.72)	1 (1.04)	0 (0.00)	
Black or African American, White	1 (0.72)	0 (0.00)	1 (2.3)	
White	133 (95.7)	91 (94.8)	42 (97.7)	
White, Native American	1 (0.72)	1 (1.04)	0 (0.00)	
Genetic status, _n_ (%)[h]				0.38[d]
GBA	15 (10.9)	8 (8.4)	7 (16.3)	
LRRK2	10 (7.2)	5 (5.3)	5 (11.6)	
PINK1	1 (0.72)	1 (1.05)	0 (0.00)	
PRKN	6 (4.3)	4 (4.2)	2 (4.7)	
VPS35	1 (0.72)	1 (1.05)	0 (0.00)	
None	105 (76.1)	76 (80.0)	29 (67.4)	
Medications, _n_ (%) [h]				
Levodopa	115 (82.7)	78 (81.3)	37 (86.0)	0.49[c]
Entacapone	3 (2.2)	2 (2.1)	1 (2.3)	0.99[d]
Carbidopa, Levodopa, and Entacapone (Stalevo)	12 (8.8)	6 (6.4)	6 (14.0)	0.19[d]
Tolcapone (excluding Stalevo)	0 (0.00)	0 (0.00)	0 (0.00)	
Apomorphine (injection, infusion, other)	0 (0.00)	0 (0.00)	0 (0.00)	
Pramipexole	21 (15.3)	14 (14.9)	7 (16.3)	0.83[c]
Ropinirole	11 (8.0)	6 (6.4)	5 (11.6)	0.32[d]
Rotigotine	6 (4.4)	2 (2.1)	4 (9.3)	0.077[d]
Rasagiline	32 (23.4)	23 (24.5)	9 (20.9)	0.65[c]
Selegiline (oral, sublingual)	3 (2.2)	2 (2.1)	1 (2.3)	0.99[d]
Amantadine (liquid, infusion)	16 (11.7)	8 (8.5)	8 (18.6)	0.088[c]
Any_medication, _n_ (%)	135 (97.1)	93 (96.9)	42 (97.7)	0.99[d]
Current comorbidities, _n_ (%)				
ALS	0 (0.00)	0 (0.00)	0 (0.00)	
Alzheimer's disease	0 (0.00)	0 (0.00)	0 (0.00)	
Arrythmia/Atrial fibrillation	7 (5.0)	5 (5.2)	2 (4.7)	0.99[d]

Table 1 continued

Arthritis	76 (54.7)	53 (55.2)	23 (53.5)	0.85[c]
B12 deficiency	15 (10.8)	7 (7.3)	8 (18.6)	0.073[d]
Cancer	6 (4.3)	5 (5.2)	1 (2.3)	0.67[d]
Congestive heart failure	1 (0.72)	0 (0.00)	1 (2.3)	0.31[d]
Crohn's disease/ulcerative colitis	1 (0.72)	1 (1.04)	0 (0.00)	0.99[d]
Depression	40 (28.8)	22 (22.9)	18 (41.9)	**0.023[c]**
Diabetes mellitus (adult onset)	6 (4.3)	5 (5.2)	1 (2.3)	0.67[d]
Diabetes mellitus (childhood onset)	0 (0.00)	0 (0.00)	0 (0.00)	
Gaucher disease	1 (0.72)	0 (0.00)	1 (2.3)	0.31[d]
Gout	2 (1.4)	2 (2.1)	0 (0.00)	0.99[d]
Hearing loss	32 (23.0)	22 (22.9)	10 (23.3)	0.96[c]
Hip fracture	0 (0.00)	0 (0.00)	0 (0.00)	
Hyper cholesterolemia (high cholesterol)	40 (28.8)	29 (30.2)	11 (25.6)	0.58[c]
Hypertension (high blood pressure)	28 (20.1)	20 (20.8)	8 (18.6)	0.76[c]
Liver	2 (1.4)	2 (2.1)	0 (0.00)	0.99[d]
Loss of smell	62 (44.6)	37 (38.5)	25 (58.1)	**0.032[c]**
Lung disease (including emphysema)	11 (7.9)	6 (6.3)	5 (11.6)	0.32[d]
Multiple sclerosis	0 (0.00)	0 (0.00)	0 (0.00)	
Myocardial infarction (heart attack)	0 (0.00)	0 (0.00)	0 (0.00)	
Normal pressure hydrocephalus	0 (0.00)	0 (0.00)	0 (0.00)	
Other	50 (36.0)	33 (34.4)	17 (39.5)	0.56[c]
Peptic ulcer disease	1 (0.72)	0 (0.00)	1 (2.3)	0.31[d]
Peripheral neuropathy	16 (11.5)	11 (11.5)	5 (11.6)	0.99[d]
Peripheral vascular disease	2 (1.4)	2 (2.1)	0 (0.00)	0.99[d]
PTSD	8 (5.8)	3 (3.1)	5 (11.6)	0.11[d]
Recreational drug use	9 (6.5)	7 (7.3)	2 (4.7)	0.72[d]
Renal insufficiency (kidney disease)	4 (2.9)	2 (2.1)	2 (4.7)	0.59[d]
Seizure, fit, convulsion or unexplained loss of consciousness	2 (1.4)	1 (1.04)	1 (2.3)	0.52[d]
Stroke, mini stroke, CVA (cerebrovascular accident) or TIA (transient ischemic attack)	2 (1.4)	0 (0.00)	2 (4.7)	0.094[d]
Thyroid disease (not cancer, including Grave's disease)	30 (21.6)	21 (21.9)	9 (20.9)	0.90[c]
UPDRS score				
Part 1, mean (sd)	8.8 (6.1)	7.4 (4.7)	11.9 (7.6)	**<0.001[a2]**
Part 2, mean (sd)	7.8 (6.9)	6.2 (5.3)	11.2 (8.7)	**0.001[a2]**
Part 3, mean (sd)[h]	21.1 (12.1)	18.8 (9.3)	26.6 (15.9)	**0.009[a2]**
Part 4, mean (sd)	3.0 (3.4)	1.1 (1.5)	7.2 (2.4)	**<0.001[a2]**

Bold italic values identify statistical significance ($p < 0.05$).

p values: [a1] = t-test, [a2] = Satterthwaite t-test, [c] = Pearson's chi-square test, [d] = Fisher's exact test.

(A) [e]Data not available for all subjects. Missing values: Genetic status = 2; Entacapone = 1; Carbidopa, Levodopa, and Entacapone (Stalevo) = 2; Tolcapone (excluding Stalevo) = 2; Apomorphine (injection, infusion, other) = 2; Pramipexole = 2; Ropinirole = 2; Rotigotine = 2; Rasagiline = 2; Selegiline (oral, sublingual) = 1; Amantadine (liquid, infusion) = 2; UPDRS Part 3 = 19; UPDRS Part 4 = 21.

(B) [f]Data not available for all subjects. Missing values: Genetic status = 3; Entacapone = 2; Carbidopa, Levodopa, and Entacapone (Stalevo) = 3; Tolcapone (excluding Stalevo) = 3; Apomorphine (injection, infusion, other) = 3; Pramipexole = 3; Ropinirole = 3; Rotigotine = 3; Rasagiline = 3; Selegiline (oral, sublingual) = 2; Amantadine (liquid, infusion) = 3; UPDRS Part 1 = 142; UPDRS Part 3 = 161; UPDRS Part 4 = 163.

(C) [g]Data not available for all subjects. Missing values: Genetic status = 2; Entacapone = 1; Carbidopa, Levodopa, and Entacapone (Stalevo) = 2; Tolcapone (excluding Stalevo) = 2; Apomorphine (injection, infusion, other) = 2; Pramipexole = 2; Ropinirole = 2; Rotigotine = 2; Rasagiline = 2; Selegiline (oral, sublingual) = 1; Amantadine (liquid, infusion) = 2; UPDRS Part 4 = 19.

(D) [h]Data not available for all subjects. Missing values: Genetic status = 1; Entacapone = 1; Carbidopa, Levodopa, and Entacapone (Stalevo) = 2; Tolcapone (excluding Stalevo) = 2; Apomorphine (injection, infusion, other) = 2; Pramipexole = 2; Ropinirole = 2; Rotigotine = 2; Rasagiline = 2; Selegiline (oral, sublingual) = 1; Amantadine (liquid, infusion) = 2; UPDRS Part 3 = 17.

factor was depression, for which there has been a great emphasis on the associations between it and PD. Depression (major depressive disorder) appeared in Parts I and II. While our study cannot definitively say if it was a pre-motor symptom of PD or if it was due to a more severe PD phenotype, depression appeared as a comorbidity of PD. Literature has shown that depression has been a prodromal symptom seen more commonly in women than in men, and as a result, women are more often misdiagnosed compared to men[15,34,35]. Moreover, in our study, perinatal depression was associated with a moderate/severe UPDRS Part II phenotype. Due to PD being more prevalent among older women, pregnancy-related factors are often neglected in PD studies, despite pregnancy having short-term and long-term effects on maternal health[36,37]. The few studies that have looked at pregnancy and PD have focused on women with young-onset PD, who usually present with a different profile[38,39]. One of the

Table 2. Women's health questionnaire responses.

	Total (n = 304) n (%)
My PD onset started…[a]	
While I was still having regular periods	52 (17.5)
While I was going through perimenopause	26 (8.8)
One year or more after my last menstrual period	219 (73.7)
Are you still menstruating[a]	
Yes	25 (8.3)
No	278 (91.7)
Have you ever been diagnosed with Premenstrual Syndrome (PMS)[a]	
Yes	34 (11.2)
No	269 (88.8)
Are you perimenopausal?[a]	
Yes	18 (6.1)
No	277 (93.9)
Has your doctor checked to see if your hormone levels have changed for perimenopause?[a]	
Yes	8 (44.4)
No	10 (55.6)
Have you experienced menopause?[a]	
Yes	264 (88.0)
No	36 (12.0)
Menses-related history	
Did/do you notice that PD symptoms improved at any part of the menstrual cycle?[a]	
Yes	7 (9.3)
No	68 (90.7)
When did/do you notice that PD symptoms improved? (check all apply)	
In the 1–7 days before my period started	1 (0.33)
During, while I was bleeding	1 (0.33)
In the 1–7 days after I stopped bleeding	4 (1.3)
In the middle of my cycle, with ovulation	1 (0.33)
None	1 (0.33)
When did you notice with symptoms worsening around menses? (check all apply)	
Medication felt less effective	8 (2.6)
Higher doses of meds were required to maintain function	4 (1.3)
More off/irregular frequency periods	10 (3.3)
N/A	32 (10.5)
Don't recall	33 (10.9)
Surgery history	
I have experienced…(check all apply)	
Total hysterectomy (removal of uterus, cervix, ovaries, Fallopian tubes, and surrounding structures)	48 (15.8)
Oophorectomy (surgical removal of one/unilateral or both/bilateral ovaries)	25 (8.2)
Mastectomy	9 (3.0)
None	193 (63.5)
Partial hysterectomy (just uterus)	33 (10.9)
Hormone-related History	
Did you start hormone replacement therapy (HRT) within the first 2 years of menopause or after receiving a hysterectomy?[a]	
Yes	84 (29.0)
No	206 (71.0)
What type of HRT have you tried?	
Estrogen	37 (12.2)
Progesterone/Progestin	10 (3.3)
Estrogen and progesterone combination	38 (12.5)
Prior to being diagnosed with PD did you use any of these types of birth control?	

Table 2 continued

	Total (n = 304) n (%)
Pill	206 (67.8)
Hormonal IUD	18 (5.9)
Copper IUD	34 (11.2)
Tubal ligation	35 (11.5)
Essure	2 (0.66)
Patch	4 (1.3)
None of these	67 (22.0)
Other	33 (10.9)
Pregnancy-related experiences	
I have experienced: (check all apply)	
In vitro fertilization	6 (2.0)
C-section	60 (19.7)
Vaginal birth	188 (61.8)
Having children prior to PD diagnosis	225 (74.0)
Having children after PD diagnosis	1 (0.33)
No children	62 (20.4)
Did you experience difficulties with:	
Conceiving (fertility)	42 (13.8)
Childbirth	35 (11.5)
Pregnancy (reaching full birth)	32 (10.5)
None	206 (67.8)
Did you have any of the following experiences prenatally, perinatally, or postnatally? (check all apply)	
Eclampsia or pre-eclampsia	15 (4.9)
Diabetes during pregnancy	7 (2.3)
Viral infection	6 (2.0)
Bacterial infection	11 (3.6)
Depression/anxiety during pregnancy	11 (3.6)
Postpartum Depression	27 (8.9)
Flair up migraines	20 (6.6)
None	209 (68.8)
Did you breastfeed?[a]	
Yes	189 (63.4)
No	50 (16.8)
N/A	59 (19.8)
Hormonal/autoimmune disorders	
Have you ever been diagnosed with any of these disorders?	
Polycystic Ovarian Syndrome	17 (5.6)
Hypothyroidism	54 (17.8)
Hyperthyroidism	19 (6.3)
Diabetes Type I	0 (0.0)
Diabetes Type II	15 (4.9)
Lupus	1 (0.33)
Rheumatoid arthritis	4 (1.3)
Migraines (no aura)	39 (12.8)

[a]Data not available for all subjects. Missing values: pd_onset = 7; still_menstruating = 1; diagnosed_with_pms = 1; perimenopause = 9; hormone_levels_for_perimenopause = 286; experience_of_menopause = 4; symptoms improved menstrual cycle = 3; hormone_replacement_therapy = 14; breastfeeding = 6.

long-term effects of pregnancy is that it has been shown to cause neurological changes in women for them to transition to a more maternal mindset[40–43]. Thus, one might hypothesize that complications that can arise during this phase, such as perinatal depression, could alter the physiological adaptions required for the transition to motherhood, resulting in a woman being

Table 3. Summary of Multivariable Logistic Regression (MLR) Results for UPDRS parts I–IV (A–D).

A. Summary of part I multivariable logistic regression (MLR) results

	Total	Mild	Moderate/Severe	Univariate p value	MLR OR (95% CI)	MLR p value
Sample size	160	112	48			
Age, mean (sd)[a]	64.4 (9.2)	64.1 (9.2)	65.0 (9.2)	0.60[a1]	1.03 (0.97, 1.09)	0.34
Years since symptom onset, mean (sd)	8.6 (6.1)	7.9 (5.7)	10.4 (6.7)	**0.017[a1]**	1.05 (0.96, 1.15)	0.27
Years since diagnosis, mean (sd)[a]	6.1 (5.3)	5.5 (4.7)	7.7 (6.2)	**0.032[a2]**		
Any PD medication, n (%)[a]	137 (85.6)	92 (82.1)	45 (93.8)	0.055[c]	3.51 (0.67, 18.30)	0.14
PTSD, n (%)	9 (5.6)	3 (2.7)	6 (12.5)	**0.022[d]**	3.72 (0.36, 37.86)	0.27
Depression, n (%)	44 (27.5)	18 (16.1)	26 (54.2)	**<0.001[c]**	9.22 (3.31, 25.71)	**<0.001**
Current comorbidities, n (%)	60 (37.5)	36 (32.1)	24 (50.0)	**0.033[c]**	3.91 (1.51, 10.14)	**0.005**
Medication felt less effective during menses, n (%)	5 (3.1)	1 (0.89)	4 (8.3)	**0.029[d]**	1.83 (0.08, 41.94)	0.7
Tubal ligation, n (%)	20 (12.5)	8 (7.1)	12 (25.0)	**0.002[c]**	2.94 (0.85, 10.15)	0.089
Vaginal birth, n (%)	106 (66.3)	66 (58.9)	40 (83.3)	**0.003[c]**	4.48 (1.10, 18.20)	**0.036**
Having children prior to PD diagnosis, n (%)	123 (76.9)	80 (71.4)	43 (89.6)	**0.013[c]**	1.00 (0.21, 4.83)	0.99
Difficulties during childbirth, n (%)	21 (13.1)	10 (8.9)	11 (22.9)	**0.016[c]**	2.15 (0.55, 8.40)	0.27
Gestational diabetes, n (%)*	5 (3.1)	0 (0.00)	5 (10.4)	**0.002[d]**		
Perinatal depression, n (%)	9 (5.6)	1 (0.89)	8 (16.7)	**<0.001[d]**	7.43 (0.63, 88.16)	0.11
Postpartum depression, n (%)	16 (10.0)	5 (4.5)	11 (22.9)	**<0.001[d]**	4.17 (0.91, 19.20)	0.067
MLR c-statistic						0.874

B. Summary of part II multivariable logistic regression (MLR) results

	Total	Mild	Moderate/Severe	Univariate p value	MLR OR (95% CI)	MLR p value
Sample size	302	246	56			
Age, mean (sd)[b]	64.7 (9.0)	64.4 (9.2)	65.7 (8.2)	0.34[a1]	1.01 (0.97, 1.06)	0.58
Years since symptom onset, mean (sd)[b]	8.8 (6.5)	7.6 (5.4)	14.0 (8.3)	**<0.001[a2]**		
Years since diagnosis, mean (sd)[b]	6.2 (5.3)	5.2 (3.8)	10.9 (7.8)	**<0.001[a2]**	1.17 (1.09, 1.25)	**<0.001**
Any PD medication, n (%)[b]	265 (87.7)	211 (85.8)	54 (96.4)	**0.028[c]**	3.28 (0.60, 18.08)	0.17
Loss of smell, n (%)	122 (40.4)	92 (37.4)	30 (53.6)	**0.026[c]**	1.27 (0.63, 2.57)	0.51
Depression, n (%)	82 (27.2)	56 (22.8)	26 (46.4)	**<0.001[c]**	2.33 (1.13, 4.80)	**0.022**
Peripheral neuropathy, n (%)	36 (11.9)	23 (9.3)	13 (23.2)	**0.004[c]**	2.27 (0.92, 5.59)	0.075
PD onset during menopause, n (%)[b]	262 (87.9)	208 (85.6)	54 (98.2)	**0.010[c]**	6.20 (0.65, 59.45)	0.11
Medication felt less effective during menses, n (%)	8 (2.6)	4 (1.6)	4 (7.1)	**0.042[d]**	1.47 (0.04, 49.75)	0.83
Mastectomy, n (%)	9 (3.0)	4 (1.6)	5 (8.9)	**0.013[d]**	4.06 (0.70, 23.68)	0.12
Perinatal depression, n (%)	11 (3.6)	5 (2.0)	6 (10.7)	**0.007[d]**	6.72 (1.35, 33.43)	**0.02**
MLR c-statistic						0.805

Table 3 continued

C. Summary of part III multivariable logistic regression (MLR) results

Sample size	141	114	27			
Age, mean (sd)[c]	64.1 (8.7)	64.0 (8.8)	64.6 (8.5)	1.00 (0.94, 1.05)	0.72[a1]	0.87
Years since symptom onset, mean (sd)	8.8 (6.0)	8.5 (5.6)	10.1 (7.2)		0.19[a1]	
Years since diagnosis, mean (sd)[c]	6.2 (5.2)	5.9 (4.6)	7.8 (7.2)	1.07 (0.99, 1.17)	0.19[a2]	0.1
Any PD medication, n (%)[c]	121 (85.8)	99 (86.8)	22 (81.5)	0.44 (0.12, 1.58)	0.54[d]	0.21
LRRK2, n (%)	11 (7.8)	6 (5.3)	5 (18.5)	6.74 (1.62, 28.00)	*0.036[d]*	**0.009**
B12 deficiency, n (%)	15 (10.6)	8 (7.0)	7 (25.9)	6.22 (1.69, 22.95)	*0.010[d]*	**0.006**
Total hysterectomy, n (%)	24 (17.0)	15 (13.2)	9 (33.3)	5.46 (1.74, 17.18)	*0.021[d]*	**0.004**
MLR c-statistic						0.791

D. Summary of part IV multivariable logistic regression (MLR) results

Sample size	139	96	43			
Age, mean (sd)[d]	64.5 (8.9)	64.3 (9.8)	65.0 (6.7)	1.01 (0.96, 1.06)	0.59[a]	0.7
Year since symptom onset, mean (sd)	8.9 (6.1)	7.5 (5.1)	12.1 (7.1)		*<0.001[a]*	
Year since diagnosis, mean (sd)[d]	6.5 (5.3)	5.1 (3.9)	9.6 (6.4)	1.17 (1.06, 1.29)	*<0.001[a]*	**0.002**
Any PD medication, n (%)[d]	135 (97.1)	93 (96.9)	42 (97.7)	1.26 (0.09, 18.67)	0.99[d]	0.87
Loss of smell, n (%)	62 (44.6)	37 (38.5)	25 (58.1)	1.58 (0.67, 3.70)	*0.032[c]*	0.29
Depression, n (%)	40 (28.8)	22 (22.9)	18 (41.9)	1.49 (0.57, 3.89)	*0.023[c]*	0.42
Medication felt less effective during menses, n (%)	5 (3.6)	1 (1.04)	4 (9.3)	2.05 (0.11, 39.34)	*0.032[d]*	0.63
Gestational diabetes, n (%)	5 (3.6)	1 (1.04)	4 (9.3)	5.59 (0.50, 62.54)	*0.032[d]*	0.16
Perinatal bacterial infection, n (%)	6 (4.3)	1 (1.04)	5 (11.6)	5.85 (0.56, 61.51)	*0.011[d]*	0.14
History of flair up migraines, n (%)	9 (6.5)	3 (3.1)	6 (14.0)	4.23 (0.78, 23.01)	*0.025[d]*	0.096
MLR c-statistic						0.782

*Variable excluded from the multivariable logistic regression.
[a]Adjusted for this variable.
[b]Adjusted for this variable.
[c]Adjusted for this variable.
[d]Adjusted for this variable.

predisposed to having PD and, even more so, a more severe PD phenotype once diagnosed. More studies are needed to parse out the exact mechanism perinatal depression has in PD risk, progression, and severity. Furthermore, within this cohort, having a natural delivery of a child was significantly associated with having a moderate/severe phenotype of PD once diagnosed. In 2020, about 69% of American women experienced a natural delivery; however, the long-term implications of natural and cesarean deliveries remain unclear for maternal health and aging[44,45]. Additionally, due to a low percentage of women having children while diagnosed with PD, little is known about if cesarean or vaginal births play a role in the risk, progression, and severity of PD, but there is one study that looked at if having PD while pregnant resulted in women going with a particular delivery method. After surveying clinicians, it was observed that being diagnosed with PD would not impact a woman's ability to have a vaginal delivery, and cesarean sections should be reserved as an alternative method of delivery, as is standard in care[46]. Other studies align with this notion and found little evidence for women with PD to have cesarean over vaginal deliveries, regardless of if a woman was currently on PD treatment and medication or not[47,48]. Overall, our study demonstrating that having a vaginal delivery was associated with a more severe PD phenotype highlights how pregnancy and postpartum choices can potentially impact women's PD risk and severity when they are diagnosed years after giving birth. Thus, subsequent studies must further examine if and how the method of child delivery, particularly when the women are not diagnosed or affected by PD, impacts PD risk, progression, and severity.

This study also found that carrying a *LRRK2* mutation was associated with a moderate/severe phenotype in Part III of UPDRS. *LRRK2* (leucine-rich repeat kinase 2) gene encodes for a ROCO family protein and is a major contributor to PD risk, as mutations in *LRRK2* have been linked to dopaminergic nerve cell death and impaired dopamine neurotransmission[49]. *LRRK2* mutations can cause autosomal dominant PD, which has been present in up to 40% of familial PD cases in certain ethnic groups[50]. Differences in PD risk and presentation between men and women with *LRRK2* p.G2019S mutations have been well characterized in the field[51–53]. While a *LRRK2* mutation carrier status is a known risk factor for PD for both men and women, overall, women have a relatively higher incidence of having a *LRRK2* p.G2019S mutation compared to men. Studies also observed differences in presentation and medication dosages between men and women with *LRRK2* mutation status[51,54]. Our study showed that the *LRRK2* mutation was associated with a more severe PD phenotype in our women cohort, opposite to previous reports combining both males and females[55,56]. Our results should be considered with caution as our sample size was small ($n = 11$), and therefore further studies are needed to determine if genetic mutations in women cause a more severe motor severity. Interestingly, only one study has briefly mentioned no differences in severity between women with positive *LRRK2* carrier status and those without, however, the majority of studies do not present sex-stratified analyses[51].

B12 deficiency is another non-sex-specific factor that was significantly associated with a higher UPDRS Part III subscore. Overall, B12 has been characterized as an important vitamin in maintaining PD nutrition. Studies have shown that low B12 is linked to cognitive impairment, higher Hoehn and Yahr scores, and dementia-related symptoms[57,58]. B12 deficiency is commonly seen in pregnant women, vegetarians, the elderly, and those who have neurodegenerative disorders[59,60]. The DATATOP study, a large two-year study of patients with early-onset PD, showed that a more rapid progression of PD symptoms occurred in those with lower B12 levels compared to those with higher levels, suggesting that increasing B12 levels may slow PD progression[61,62]. Therefore, it is reasonable to observe that those with a moderate/severe phenotype in our study had a B12 deficiency compared to those

with mild PD severity. However, this factor needs to be fully explored in future studies to determine if B12 is a validated risk factor or modifies PD severity, as low B12 levels may be due to PD itself. While this association appeared in Part III (motor examination), interestingly, there was also a trend of significance in Part II (motor experiences of daily living) of this subcohort (OR = 2.27 (1.13, 4.80) $p = 0.075$). Since literature has suggested that B12 deficiency has been associated with peripheral neuropathy[63,64], this observation of statistical significance in our cohort suggests a possible connection between B12 deficiency and the trend of peripheral neuropathy in women with a more severe PD phenotype.

In our study, we defined total hysterectomies as the removal of the entire uterus, cervix, and ovaries/fallopian tubes. Although the removal of the ovaries and fallopian tubes is not included in the definition of total hysterectomies, they are often included in the procedure based on the patient's medical history. Total hysterectomies were significantly associated with a more severe PD phenotype in the PD GENEration questionnaire respondents. Hysterectomies are one of the most commonly performed procedures done in women (second after cesarean sections), and they treat gynecologic malignancies and benign gynecologic diseases[65,66]. About 1 in 3 women in the United States have a hysterectomy by the age of 60[67], and one study approximates that about 600,000 of these procedures are performed annually in the United States[68]. Removal of the ovaries leads to patients taking exogenous hormones, which have been studied in relation to PD risk. However, across these studies, there is no conclusive answer to if exogenous hormones contribute to PD risk. One study found that hysterectomies, with or without unilateral oophorectomy (removal of one ovary), were significantly associated with PD risk[25]. Other studies found similar results with women being at a higher risk for PD if they either had unilateral or bilateral oophorectomies before experiencing menopause or if they used estrogen alone after a hysterectomy[18,19,30]. On the other hand, one study found that anemia, a condition that is more common in women and can lead to hysterectomies, was associated with PD risk in women, even after adjusting for hysterectomies, which indicates that the procedure is not a confounding variable that impacts PD risk[69,70]. In our study, the association between PD severity and hysterectomies with the removal of ovaries indicates that this procedure is not only a risk factor but also a modifier for the severity of the disease itself. It is critical for further studies to elucidate a definitive answer on the implications partial and total hysterectomies have in increasing the risk of PD and modulating PD severity, especially since they are prevalent procedures in gynecological care.

This is an exploratory study that addresses sex-specific experiences from menses to menopause; however, there are some limitations. First, since this study primarily gathers WSHF history from a questionnaire, like other survey studies, it relies heavily on the response rate. Our response rate is low, at 31.5%, while 60–80% is generally expected[71,72]. Although we are below average, a further limitation of our questionnaire response rate is selection bias as our questionnaire was deployed via email to PD GENEration, leaving those who are neither able to join PD GENEration nor have regular email access unable to participate. As PD GENEration is rapidly growing, we hope to continue deploying this questionnaire to more women with PD. As this is an exploratory study for the purpose of hypothesis generation, we presented our results without adjusting for multiple comparisons. Though given the large number of associations tested in this study, there is the possibility of Type I errors. This study used a questionnaire based on previous literature looking at women's health and PD and WSHFs that are of interest to researchers and clinicians looking at sex differences. Because of the study design and variable selection approach, a causal relationship between sex-specific factors and PD cannot be established. It is possible

that some of our findings may have been affected by confounding or reverse causality. Further studies are needed to expand the sex-specific factors to analyze, ideally based on Directed Acrylic Graphs (DAGs). Furthermore, as we implemented this questionnaire retrospectively without a medical history for each participant, the study cannot define the causality of PD severity. This limits the definitive conclusiveness of the role the discussed factors have in PD severity, leaving future studies to validate these findings. We have also begun distributing this questionnaire across North America Cleveland Clinic campuses. Currently, this questionnaire has been circulated nationally in the United States, and we are expanding our efforts to Latin America through the Latin American Research Consortium (LARGE-PD)[73]. This international effort will help better understand WSHF differences between regions and sociocultural norms, overcoming the lack of generalizability this study currently faces regarding women with PD in various environments. These greater efforts will hopefully overcome the low response rate (due to selection bias) currently present in this study.

Another limitation is that this study uses PD severity. PD severity varies across literature and clinical standpoints, as many factors contribute to categorizing PD patients' current health-related quality of life. We implemented Martinez-Martin et al.'s thresholds for severity, but because our study uses only one UPDRS time-point for analysis, this could be a misrepresentation of the respondents' PD severity phenotype and result in misclassification bias. The UPDRS assessment can be influenced by many factors, such as the time medication was taken before the assessment, stress, "on" and "off" states, and whether the participant or clinician answered the questions[74]. Thus, there is a lack of generalizability as we are using a one-time assessment as the basis of severity alongside participant-reported outcomes. A larger population of women with PD is needed to validate the findings presented in this study. Further studies will be needed to determine whether these thresholds represent the moderate/severe PD phenotype and use multiple UPDRS assessments. Progression of PD is another critical factor in the health-related quality of life, and it varies from person to person. Thus, studying the effects of WSHFs in PD progression will significantly benefit women with PD and the scientific community.

Lastly, the sample size is another limitation of this study. Due to the overall $n = 304$, we have small sample sizes between our phenotype groups when looking at each WSHF. A larger sample size would allow us, with greater statistical power, to look at smaller effect sizes each WSHF has with PD severity. With a higher response rate, we hope to overcome this limitation by validating our findings in a larger sample size of women with PD.

Despite these limitations, our study has considerable strengths. We created a scientific questionnaire that addresses multiple WSHFs, some of which have never been addressed before[18]. Our questionnaire was a collaboration between neurologists, PD experts, and women's health specialists and was validated for comprehension at Cleveland Clinic. Unlike other previous questionnaires, this one is publicly available for the sole purpose of incorporating WSHF questions into routine PD assessments. As many questionnaires used in the clinic are focused on gender-neutral factors, we hope this study sheds light on the purpose of acknowledging sex-specific aspects in the pursuit of bettering the treatment and care for those suffering from PD. Furthermore, this study demonstrates the importance that sex-specific factors have and that the field must further explore the role of these factors in PD risk and severity.

Another strength of this study is that we look at exogenous hormone therapy, such as estrogen, in relation to PD severity. Previous studies have considered estrogen as a protective factor against PD; although this has not been reproducible across the field, there are limited studies that have addressed estrogen in PD severity[28,29,31,33,75]. While only 28% of our cohort utilized

exogenous hormone replacement, we did not see exogenous hormone replacement associated with the mild phenotype. Moreover, we did not see any birth control forms associated with PD severity, despite the majority of participants having a history of use. Further studies are needed to better understand the role of estrogen and hormones in PD severity.

Another strength of this study is that it includes genetic, demographic, sex-specific, and clinical variables when looking at PD severity. Previous literature that looked at WSHFs used electronic medical records or a questionnaire that didn't incorporate genetics, leading them to be neglected in PD etiology. We had a moderate cohort of those with *LRRK2* and *GBA* mutations. Our study showed that amongst our cohort, having a *LRRK2* genotype was significantly associated with a moderate/severe phenotype. Thus, including genetic data in these models elucidates that genetic predisposition may be related to having a more severe PD phenotype in women.

Overall, this study used a questionnaire deployed across the United States to determine what WSHFs women with PD experienced. With this questionnaire, we were able to create a dataset of 304 women and their genetics, women-specific experiences, and clinical history. We found that by creating score thresholds for each UPDRS subpart, we could determine if WSHFs were associated with PD severity when adjusted for age, age at diagnosis, and PD medication. We found that depression and vaginal birth (Part I); depression and perinatal depression (Part II); *LRRK2* mutation status, B12 deficiency, and total hysterectomy (Part III) were significantly associated with a moderate/severe PD phenotype compared to a mild phenotype. This is one of the few studies that emphasize the role of WSHFs in PD. Future studies with a larger population of diverse women are needed to validate these findings, preferably with multiple UPDRS scores and a more detailed clinical history, as this study is an exploratory effort to address if WSHFs affect PD severity in women with PD. In regards to the limitations stated previously, such as the variables analyzed, causality, and the generalizability of findings, the results of this study should be considered with caution. The results observed in this study can shape future studies with larger cohorts to incorporate sex-specific factors when building models and explore the casualty of these factors as seen in other PD studies[76]. Nevertheless, this study sets the groundwork for acknowledging the role WSHFs in conjunction with non-sex-specific factors may play in PD and the potential benefit the scientific community can gain for therapeutics and clinical guidance if we further investigate the role sex-specific factors have in PD etiology.

METHODS

Questionnaire development and implementation

With the gap in information regarding WSHFs and PD, we developed and implemented a nationally distributed questionnaire, which is often used to generate large datasets of patient-reported outcomes within the epidemiological field[77]. Our previous publication explains how we developed this questionnaire in detail[78]. In summary, we compiled a list of WSHFs based on their possible association with the disease or their lack of inclusion in PD data thus far. Then, neurologists and movement disorder specialists at Cleveland Clinic along with PD and women's health experts advised on further modifications of the questionnaire. It was then formatted using a combination of short-text (age and additional comments to be typed if needed), check-boxes, and Likert-type rating scales for symptom changes with the guidance of the Cleveland Clinic Quantitative Health Sciences patient-reported outcomes team. Our primary concern was to limit recall bias, as our subjects skewed toward being above the age of 50 and post-menopausal, so we implemented branching logic, allowing the participant to answer questions that are

relevant based on their age of diagnosis (during menses, before or after menopause) and women-specific experiences (including birth control, pregnancies, surgeries, and hormone-replacement therapy) that can occur around that age range. The questionnaire, which can be found in its entirety in our previous work[78], is on REDCap, a secure web application used for building online surveys and databases[79]. To validate that our questionnaire was comprehensible and could be completed in a reasonable time, movement disorder specialists at CCF administered it with a tablet in the waiting room to ten women with PD and verified that these subjects were able to answer the questions comprehensively in a timely manner. The participants took an average of 20 min to complete the questionnaire.

The Parkinson's Foundation launched the PD GENEration study (PD GENE; ClinicalTrials.gov identifier: NCT04057794), which provides genetic testing for seven PD-related genes by a CLIA-certified laboratory and genetic counseling at multiple locations in North America at no cost to the individuals diagnosed with PD. At the same time, they collect critical clinical and demographic information from each patient[21]. Each participant is seen and clinically assessed by a movement disorder specialist, who inputs their demographic and clinical data. We have partnered with the Parkinson's Foundation to implement our questionnaire because, in the past, PD GENEration has successfully distributed various research questionnaires from other institutions to patients on their email list who consented to receive questionnaires designed for research[80,81]. Starting in mid-November 2021, PD GENEration released our questionnaire cross-sectionally to women with PD who had participated in PD GENEration in order to retrospectively inquire about their women-specific experiences and how these experiences may have impacted their PD health-related quality of life. An email reminder was sent in mid-December, and the questionnaire closed on December 2021. This study was performed with written informed consent under an IRB regulated protocol.

PD GENEration has IRB approval (IRB # 20-596) to share de-identified patient data (genetics, clinical information, and demographics) with us in addition to the responses to our questionnaire for research purposes. PD GENEration exported the participants' responses alongside their genetic and clinical data. This study is approved by Cleveland Clinic (IRB # 21-1138).

Quality control
As this is a patient-reported study, we filtered the variables in the questionnaire and demographic data from PD GENEration, and we removed variables where at least 80% of responses were missing or "not available".

MDS-UPDRS severity scale
The Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the most widely used clinical scale for rating motor and non-motor symptom severity in PD. The MDS-UPDRS has four parts: I: Non-motor Experiences of Daily Living; II: Motor Experiences of Daily Living; III: Motor Examination; IV: Motor Complications[82]. At the time of recruitment, PD GENEration had either a clinician or study coordinator administer the MDS-UPDRS.

Missing data in clinical rating scales is problematic because assessments are usually time-locked to an office visit and cannot be retrospectively filled in with reliability. To overcome the missingness in the dataset, we followed the protocol set by Goetz et al. that established thresholds for the maximum number of scores that can be missing from each part. Goetz et al. found that only one missing item from Part I, two from Part II, seven from Part III, and zero from Part IV can be allowed for an individual to be included in subsequent analyses[83]. If the number of missing items is within the threshold, we followed a protocol implemented by Goetz et al. to create a prorated total score for UPDRS Parts I-IV[83].

Following these adjustments, we divided our cohort into "mild" and "moderate or severe" UPDRS groups based on the maximum triangulation cut-off values stated in Martinez-Martin et al.[84]. We decided to group them by "mild" vs. "moderate/severe" due to the low number of women with a "severe" UPDRS score. Thresholds for moderate/severe were Part I: >21; Part II: >29; Part III: >58; and Part IV: >12. Mild vs. moderate/severe distributions for each UPDRS part are presented in Supplementary Table 3.

Statistical analysis
Demographics, clinical characteristics, genetics, questionnaire responses, and UPDRS scores were summarized using descriptive statistics. Comparisons were made using t-test or Satterhwaite t-test (if assumption of equal variance was not met) for continuos variables and chi-square or Fisher's exact test for categorical variables. Univariate logistic regression models were constructed for each UPDRS subpart to evaluate the associations between PD severity and WSHFs, genetics, and clinical variables. For "check all that apply" questions, dummy variables were created for each response option. Variables with fewer than five positive responses were not included in the analysis. Furthermore, for Likert-type questions, "N/A" and "Don't recall" were set to missing. Questions were excluded if more than 80% of responses were "N/A" or "Don't recall." As our dataset contains novel variables that have neither been explored nor been well understood in the PD field so far, we first sought to see which variables may be associated with predicting PD severity using a univariate logistic regression model. If a variable had a very low or high prevalence, the Firth method was used in our regression modeling[85,86]. For each UPDRS subpart, multivariable logistic regression models were constructed from the variables of interest that were gathered from the univariate regression models. These included age, disease duration, and medication, as determined a priori, along with WSHF variables that were significant in the univariate logistic regression models at $p < 0.05$. Model assumptions and multicollinearity were assessed. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC). Statistical significance was established throughout at $p < 0.05$.

Reporting summary
Further information on research design is available in the Nature Research Reporting Summary linked to this article.

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The authors declare no competing interests.

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