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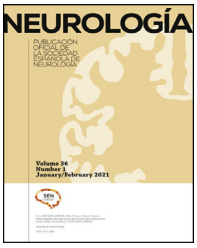

ORIGINAL ARTICLE

Effect of sex on the progression of non-motor symptoms in Parkinson's disease: A registry-based cohort study

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KEYWORDS
Sex;
Non-motor symptoms;
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Abstract
Introduction: Differences in the trajectory of non-motor symptoms (NMS) between male and female Parkinson's disease (PD) patients over the course of the disease are not well-understood.
Methods: PD patients were rated with Non-Motor Symptom Scale (NMSS) at two time points with a median follow-up of 3.8 years (IQR 2.1—5.6 years). Sex, age, disease duration, Unified Parkinson's Disease Rating Scale and doses of PD-related medication were registered. Linear mixed models (LMMs) and multinomial logistic regression (MLR) models were fitted to explore the association of sex with changes in NMSS domains over time.
Results: Eighty-seven PD patients (30 females and 57 males) were enrolled. Baseline demographic and clinical characteristics were similar between female and male PD patients. The mean increase in NMS frequency and severity over time was non-significant, as well as the interaction term for *disease duration* × *sex*. However, gastrointestinal symptoms worsened in both males and females. According to the minimal detectable change of NMSS, <50% of PD patients experienced changes at follow-up beyond measurement error of the scale. Male sex predicted sexual function worsening (adjusted OR = 10.1, $p = 0.038$). Also, PD patients with more severe symptoms at baseline had increased odds of improving over time. However, high initial scores in attention/memory and cardiovascular domains also posed individuals at a higher risk of symptom worsening (OR [95% CI] = 1.4 [1.0-1.8], $p = 0.034$ and OR [95% CI] = 2.1 [1.2-3.7], $p = 0.01$, respectively).

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Conclusion: NMS progression over the disease course in PD shows large inter-individual variability without observable effect of sex.

PALABRAS CLAVE
Sexo;
Síntomas no motores;
Enfermedad de Parkinson;
NMSS;
Longitudinal;
Evolución

Efecto del sexo en la progresión de los síntomas no motores en la enfermedad de Parkinson: un estudio de cohorte basado en registro

Resumen
Introducción: En la enfermedad de Parkinson (EP) se desconocen las diferencias que existen entre hombres y mujeres respecto a la evolución natural de los síntomas no motores (SNM).
Métodos: Se administró la Escala de Síntomas No Motores (NMSS) a pacientes con EP dos veces con un tiempo de seguimiento de 3.8 alos (rango intercuartil: 2,1 - 5,6 años). Se registraron el sexo, la edad, la duración de la enfermedad, la escala unificada de calificación de la enfermedad de Parkinson (UPDRS) y las dosis de medicación relacionada con la EP. Se ajustaron modelos mixtos lineales (LMM) y modelos de regresión logística multinomial (MLR) para explorar la asociación del sexo con cambios en los dominios NMSS a lo largo del curso de la enfermedad.
Resultados: Se seleccionaron 87 pacientes con EP (30 mujeres y 57 hombres) del registro de cohorte. Las características clínicas y demográficas iniciales fueron similares entre hombres y mujeres con EP. El incremento medio de la frecuencia y la gravedad del SNM a lo largo de la enfermedad no fue significativo, y tampoco la interacción entre la duración de la enfermedad y sexo. No obstante, los síntomas gastrointestinales empeoraron de media tanto en hombres como en mujeres. Según los valores del cambio mínimo detectable del NMSS, <50% de los pacientes con EP experimentaron cambios en el seguimiento más allá del error de medición de la escala. El sexo masculino predijo el empeoramiento de la función sexual (OR ajustado = 10,1, p = 0,038). Los pacientes con EP con síntomas más graves al inicio tenían mayor probabilidad de mejorar con el tiempo. Sin embargo, las puntuaciones iniciales altas en los dominios Atención/Memoria y Cardiovascular estaban asociadas a un mayor riesgo de empeoramiento de los síntomas (OR [IC del 95%] = 1,4 [1,0-1,8], p = 0,034 y OR [IC del 95%] = 2,1 [1,2-3,7], p = 0.01, respectivamente).
Conclusión: La progresión de los SNM a lo largo del curso de la enfermedad en la EP muestra una gran variabilidad interindividual sin que existan diferencias significativas entre hombres y mujeres en su evolución.

Introduction

Patients with PD develop a wide range of non-motor manifestations during the course of the disease, some even preceding the onset of motor symptoms.[1,2] It is increasingly acknowledged that the burden of non-motor symptoms (NMS) impacts on the quality of life (QoL) presumably to a greater degree than motor symptoms.[3—6] However, there is no standardized international consensus for their diagnosis in clinical practice. In that sense, some useful questionnaires have been developed, such as the Non-Motor Symptoms Scale (NMSS), which is a validated questionnaire to assess NMS in PD.[7] It individually evaluates the frequency and severity of nine domains of NMS such as cardiovascular symptoms, sleep disorders and fatigue, hallucinations, mood, attention and memory, or dysautonomia (urinary, sexual and gastrointestinal dysfunction). Additionally, the miscellaneous domain assesses pain, taste/smell and thermoregulatory aspects. A NMSS total score is finally calculated as the sum of all domains.

There is now a growing body of evidence regarding sex differences in the prevalence of NMS in PD.[8—10] Several cross-sectional studies have shown that fatigue, pain or constipation are more frequent in female than male PD patients.[11] On the other hand, male PD patients report increased daytime sleepiness, sexual dysfunction, and urinary disturbances.[12,13] Moreover, PD males show worse executive functions, whereas females display altered visuospatial functions.[14,15] Female PD patients are also more prone to suffer mood disorders and depression.[16,17] Although the cross-sectional sex differences have been deeply explored, there is scarce evidence about the natural evolution of NMS in male vs. female PD patients during disease course. Furthermore, the studies assessing the progression of NMS have provided conflicting results, some showing significant increase in NMS overtime,[18,19] whereas others have observed that NMS remain stable[20,21] or even improve.[22]

In this work, female and male PD patients were rated with NMSS at two time points with a median time interval

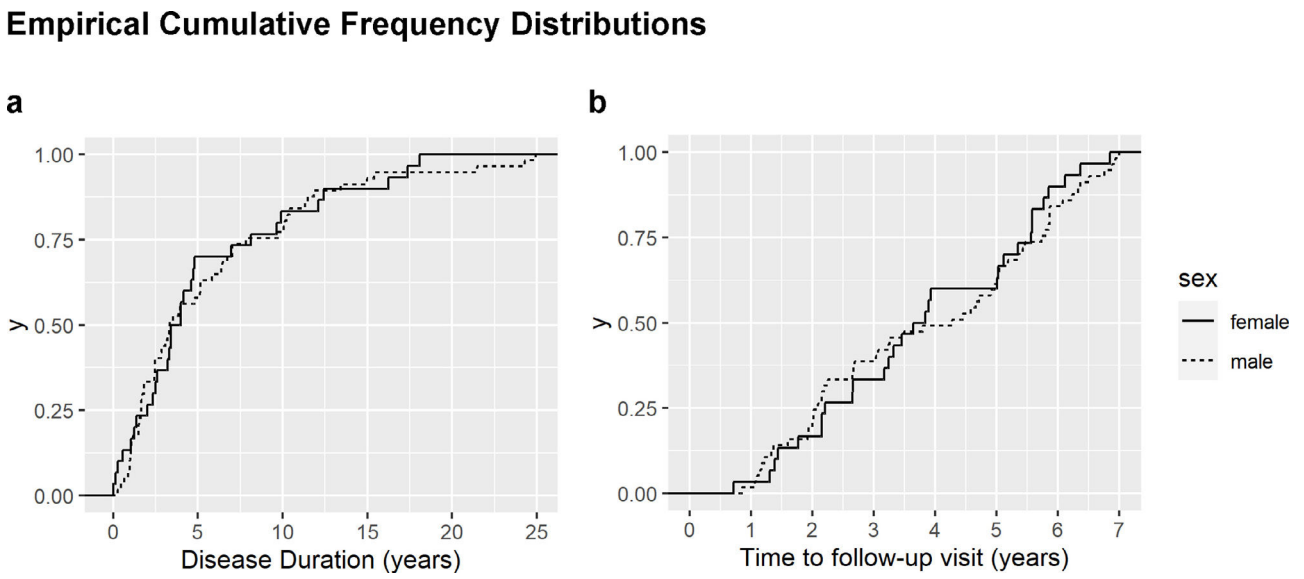

Figure 1 Empirical cumulative frequency distributions of disease duration (a) and time to follow-up visit (b) in female (solid line) and male (dashed line) PD patients. Each graph shows the running total proportion of PD patients that falls below the upper boundary at a given time point.

of 3.8 years between visits (range 0.7—7 years) to determine sex differences in the longitudinal evolution of NMS during disease course and its relationship with baseline NMS scores, motor impairment and changes in PD-related medication.

Participants and methods

Study design and participants

The study was conducted within the framework of a registry-based cohort study from Cruces University Hospital. For this ancillary study, criteria for eligibility were: (a) to have clinical diagnosis of PD according to UK Parkinson's disease Society Brain Biobank Diagnostic Criteria; (b) to have two visits with complete evaluation of NMSS questionnaire; (c) no missing data in age, sex, disease duration or Unified Parkinson's Disease Rating Scale (UPDRS), part III (see Supplementary Material).

Included participants completed two visits. Baseline visits were conducted between February 2010 and April 2016. Time interval for the follow-up visit varied among PD patients (from 0.7 years to 7 years, Fig. 1). Last visit was conducted on October 2017. Data analyses were conducted from May 2022 to August 2022. Participants gave their consent prior to their participation, in accordance with the tenets of the Declaration of Helsinki. The OSI Ezkerraldea-Enkarterri-Cruces ethics committee approved the study protocol.

Clinical data collection

We collected baseline data including the following demographics and clinical variables: age, sex, and disease duration. At each visit, we also recorded daily dose of levodopa, dopamine agonists (DA), catechol-O-methyltransferase inhibitors, monoamine oxidase type B inhibitors, and anticholinergic drugs. Afterwards, levodopa equivalent daily dose (LEDD) was calculated for PD-related medication. LEDD for levodopa (levodopa-LEDD) and LEDD for dopamine agonists (DA-LEDD) were also calculated. In each visit, disease severity was assessed with UPDRS and NMS were assessed with NMSS.

Statistical analysis

All the analyses were performed using the RStudio software (version 2022.07.0). We described baseline features of the study population using absolute and relative frequencies for categorical variables, and mean and standard deviations for quantitative variables. For NMSS scores, we used medians and IQR to describe baseline features of the study due to the ordinal nature of the variable. Normal distribution of variables was tested with Shapiro—Wilks, and *T*-test or Mann—Whitney *U* test were used for hypothesis testing of normally and non-normally distributed quantitative variables, respectively.

To evaluate whether the progression of NMS was different between male and female PD patients, we first fitted linear mixed-effects models (LMM) using the *lme4* and *lmerTest* packages. We introduced *disease duration* × *sex* interaction as the main fixed effect, adjusted for age at baseline. Log-transformed values of each NMSS domain were introduced as the outcome variable to meet model assumptions. A random intercept for subjects was used and its intraclass correlation coefficient was calculated. Then, multinomial logistic regression (MLR) analyses were computed with *nnet* package. Minimally detectable changes (MDC) of NMSS (see[23]) were used as cutoffs to assign PD patients to three evolution subgroups: ''improvement'' if PD patients decreased the NMS at follow-up beyond MDC, ''worsening'' if symptoms increased beyond MCD and ''stable'' if symptom scores

Table 1 Demographics and clinical characteristics of PD patients at baseline.

	Median (*Q*1—*Q*3)	Range
All PD patients		
Time to follow-up	3.8 (2.1—5.6)	0.7—7.0
Age (years)	66.5 (60.9—72.2)	40.3—83.1
Disease duration (years)	3.4 (1.7—8.0)	0—24.9
Age at disease onset (years)	60.2 (54.7—67.8)	37.9—82.7
UPDRS I	2 (0—3.5)	0—8
UPDRS II	10 (7—14)	0—30
UPDRS III	27 (23—32)	10—58
UPDRS IV	2 (1—4)	0—13
LEDD, total (mg)	700 (300—1100)	0—2780
LEDD, levodopa (mg)	400 (50—600)	0—1440
LEDD, DA (mg)	150 (0—300)	0—860
Female PD patients		
Time to follow-up	3.7 (2.3—5.5)	0.7—6.8
Age (years)	66.5 (59.6—70.3)	45.4—77.8
Disease duration (years)	3.7 (2.1—7.8)	0—18.1
Age at disease onset (years)	58.8 (54.7—66.1)	37.9—74.1
UPDRS I	2 (0—3.5)	0—8
UPDRS II	10 (7—14)	0—30
UPDRS III	27 (23—32)	10—58
UPDRS IV	2 (1—4)	0—13
LEDD, total (mg)	700 (300—1100)	0—2780
LEDD, levodopa (mg)	400 (50—600)	0—1440
LEDD, DA (mg)	150 (0—300)	0—860
Male PD patients		
Time to follow-up	4.3 (2.1—5.7)	0.8—7.0
Age (years)	66.5 (62.5—73.8)	40.3—83.1
Disease duration (years)	3.3 (1.7—7.8)	0.3—24.9
Age at disease onset (years)	60.6 (53.9—69.0)	38.4—82.7
UPDRS I	2 (0—3)	0—8
UPDRS II	11 (7—15)	0—24
UPDRS III	27 (24—32)	16—49
UPDRS IV	2 (1—3)	0—10
LEDD, total (mg)	725 (300—1112)	0—2780
LEDD, levodopa (mg)	400 (112.5—631.25)	0—1150
LEDD, DA (mg)	165 (0—305)	0—700

Abbreviations: DA, dopamine agonist; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale.

remained within the limits of MCD. ''Stable'' group was used as the reference group. Unadjusted MLR models assessed the effect of sex on symptom progression subtype at follow-up visit. Multivariable MLR models were used to adjust for baseline measurement of the dependent variable, age at baseline, and disease duration at baseline. Statistical significance was set at $p < 0.05$.

Results

Baseline demographics and clinical characteristics

Eighty-seven patients with PD were selected for this study from the original cohort, including 57 males (65.5%) and 30 females (30.5%). Table 1 shows baseline demographics and clinical characteristics of male and female PD patients. Briefly, PD patients showed mild to moderate motor manifestations (UPDRS III ≈28) with a median disease duration of 3.4 years (range 0—25 years). Forty-one percent of patients had disease duration lower than 3 years, and about a third presented disease duration longer than 6 years (Fig. 1a). Twenty-one out of 87 PD patients (24%) were not receiving levodopa treatment, and 64.3% received DA therapy at baseline.

No statistical differences were found between males and females in baseline characteristics, including age, age at disease onset, disease duration, disease severity, LEDD and dose of levodopa or DA therapy. Still, males had slightly higher scores in motor-related activities of daily living compared to females (UPDRS II, $p = 0.07$).

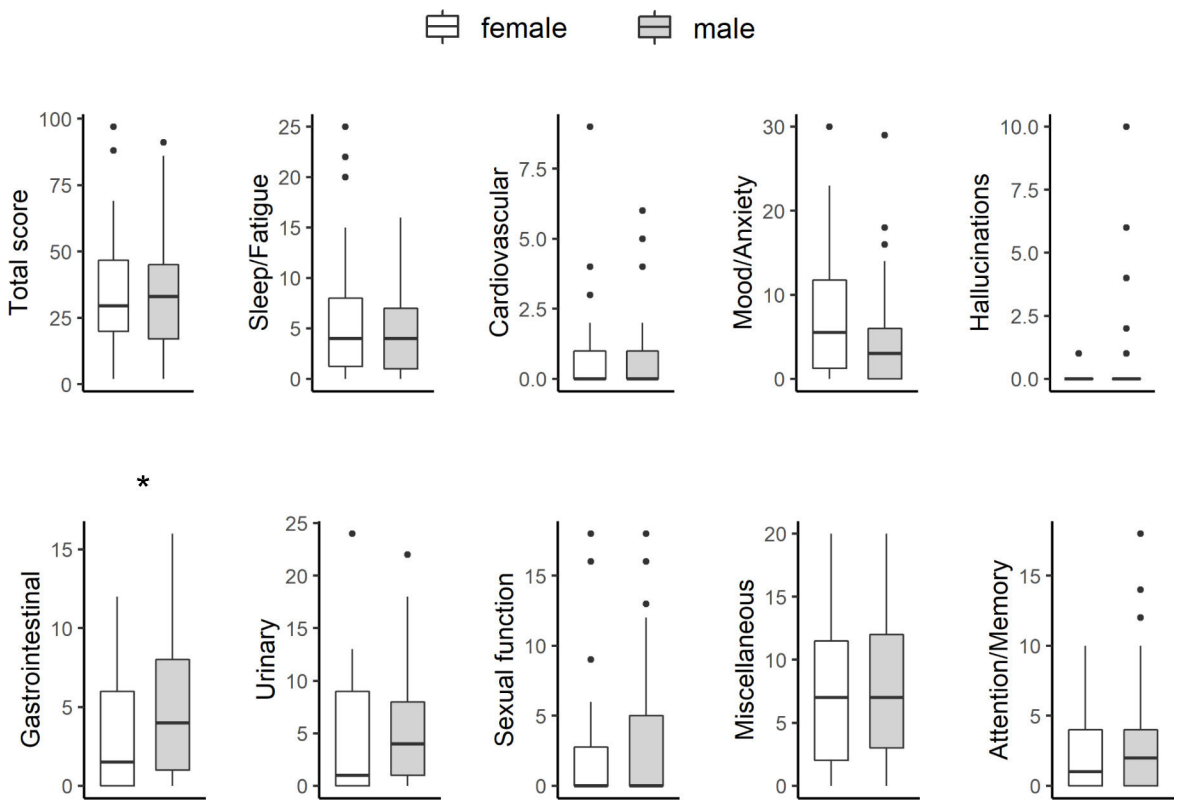

Figure 2 Boxplots of baseline NMSS scores in female and male PD patients. *$p < 0.05$.

Baseline NMSS scores

Fig. 2 and Table S1 show baseline NMSS scores. At baseline, miscellaneous, mood/apathy, sleep/fatigue and gastrointestinal tract domains were the symptoms with higher prevalence. Statistically significant differences were observed within the gastrointestinal domain between female and male PD patients ($p = 0.04$), but not in the remaining NMSS domains. Subitem analysis showed that this difference was because male PD subjects scored significantly higher for the severity and frequency of sialorrhea. Contrarily, female PD patients showed higher baseline scores in mood/anxiety domain, and subitem analysis revealed significantly increased nervousness and depression in female compared to male PD. Although median urinary and sexual function scores were close to zero in both males and females, the variability among patients was notorious.

Evolution of disease-related variables over time

The time interval between baseline and follow-up visit ranged from 0.7 years to 7 years. The median time to follow-up was 3.7 (IQR 2.3—5.5) years for females and 4.3 (IQR 2.1—5.7) years for males ($p = 0.954$). Fig. 1 shows the empirical cumulative frequency distribution of time to follow-up.

The LMMs indicated that motor impairment (UPDRS III) significantly increased over the course of the disease ($\beta = 1.03$, SE 0.24; $p < 0.0001$) without sex differences. Regarding medication, as expected, levodopa-LEDD ($\beta = 49.4$, SE 14.0; $p < 0.001$) and DA-LEDD ($\beta = 12.7$, SE 4.2; $p = 0.003$) increased with time, as well as total LEDD ($\beta = 23.6$, SE 7.4; $p = 0.002$). Males showed a trend towards lower increase in DA-LEDD over time ($\beta = -9.4$, SE 4.5; $p = 0.06$).

Sex differences in NMS progression throughout disease course

In LMM, the estimated coefficients for the interaction term *disease duration* × *sex* were non-significant for all NMSS domains, meaning that the natural evolution of NMS did not differ between males and females. A dissimilar trend was acknowledged in NMSS total score progression, male PD patients showing an increased rate of progression compared to females, probably influenced by a steeper increase of urinary symptoms in males (Fig. 3). Furthermore, most domains did not significantly change over time, except for the gastrointestinal tract domain, which significantly increased as the disease progressed. We also observed that age at baseline was significantly associated with the progression of total NMSS, cardiovascular, perceptual problems/hallucinations, digestive and urinary problems.

For the fitted models, we calculated marginal and conditional R^2, the former providing the variance explained only by the fixed effects, whereas the latter providing the variance explained by both fixed and random effects. As evidenced by these metrics, fixed effects explained little to none of the variance in the progression of NMS (<10% in most cases), whereas including random effects considerably increased it. We further estimated the variance of

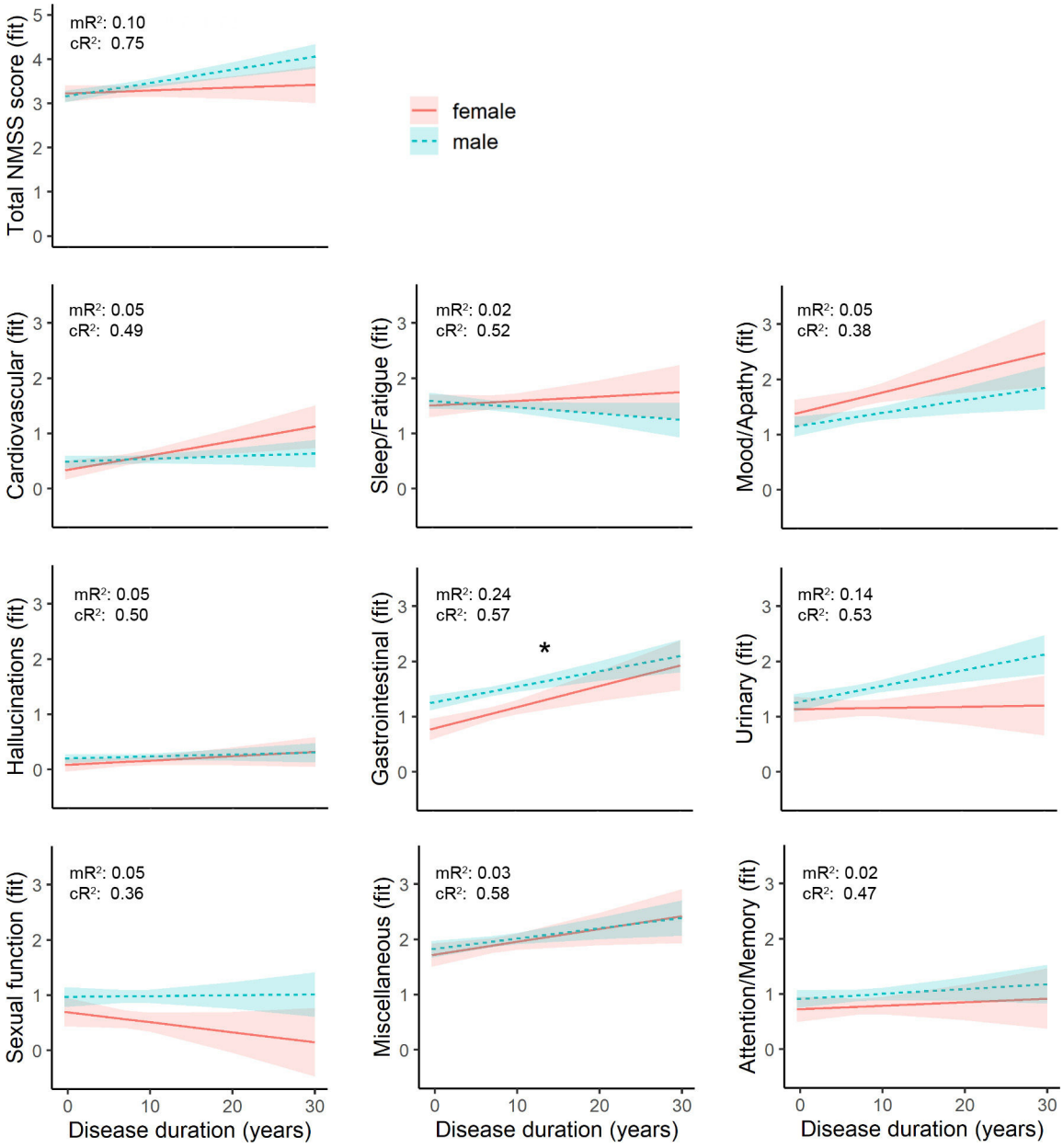

Figure 3 Parameter estimates of non-motor symptoms progression derived from linear mixed-effect models by sex. Values in *y*-axis represent the log score of the predicted outcome variable. mR^2 is the proportion of the variance explained by fixed effect (disease duration, sex, *disease* × *sex* interaction, age at baseline) and cR^2 is the proportion of variance explained by the fixed effects and random effects. *Abbreviations*: cR^2, conditional R^2; mR^2, marginal R^2. *$p < 0.05$ for disease duration factor. The effect of sex was non-significant.

subject effect on the overall level of NMS progression. The percentage of the variance explained by the random effects (subject-specific variation) was 65% for NMSS total score, and between 33% and 55% in single NMSS domains, meaning that a large proportion of variance in the dependent variable was accounted for by between-subject variance, i.e., the heterogeneity between participants. Nevertheless, a substantial proportion of the variance remained unexplained.

Further adding total LEDD as fixed effect to LMMs did not result in improved fit, nor it was significantly associated with the outcome variables. The results from a sub-analysis adding levodopa-LEDD or DA-LEDD as fixed effect were consistent. The only exception was mood/apathy domain, where both LEDD for levodopa and for DAs were independently associated with changes in mood/apathy domain. For every 100 mg of levodopa-LEDD increase, mood/apathy score increased 0.9 points ($p < 0.001$), and for every 1 g of DA-LEDD increase, mood/apathy decreased −1.5 points ($p = 0.001$). Finally, LMMs showed that the progression of motor manifestations was associated with the evolution of NMS in 7 out of the 9 domains of NMSS (exceptions were perceptual problems/hallucinations and urinary domains), and with NMSS total score.

Table 2 Frequency of subjects showing MDC in NMSS domains at follow-up visit.

	MDC Cutoff	MDC *n* (%)	Stable *n* (%)	Improvement *n* (%)	Worsening *n* (%)
Cardiovascular	1.71	33 (37.9)	54 (62.1)	14 (16.1)	19 (21.8)
Sleep/fatigue	4.31	19 (21.8)	68 (78.2)	9 (10.3)	10 (11.5)
Mood/apathy	4.28	28 (32.2)	59 (67.8)	15 (17.2)	13 (14.9)
Perceptual problems/hallucinations	2.19	35 (40.2)	52 (59.8)	18 (20.7)	17 (19.5)
Attention/memory	3.02	3 (3.4)	84 (96.6)	2 (2.3)	1 (1.1)
Gastrointestinal tract	3.40	27 (31)	60 (69)	15 (17.2)	12 (13.8)
Sexual function	3.35	22 (25.3)	65 (74.7)	14 (16.1)	8 (9.2)
Urinary	3.6	30 (34.5)	57 (65.5)	16 (18.4)	14 (16.1)
Miscellaneous	3.62	31 (35.6)	56 (64.4)	17 (19.5)	14 (16.1)
NMSS total score	13.81	35 (40.2)	52 (59.8)	16 (18.4)	19 (21.8)

MDC of NMSS domains have been determined by Martinez-Martin et al.[23] Using these cutoff values, PD patients were allocated in three subgroups: ''stable'' if change score at follow-up was below MCD, ''improvement'' if the change score was lower than MCD at follow-up, and ''worsening'' if change score was larger than MCD at follow-up visit. *Abbreviations*: MCD, minimally detectable change; NMSS, Non-Motor Symptoms Scale.

Table 3 Association of baseline NMS measurement with symptom improvement or worsening in PD.

	Improvement			Worsening		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Cardiovascular	4.53	2.02—10.16	<0.001	2.12	1.20—3.73	0.010
Sleep/fatigue	1.48	1.21—1.80	<0.001	1.12	0.93—1.35	0.244
Mood/apathy	1.47	1.23—1.76	<0.001	1.06	0.91—1.23	0.460
Gastrointestinal tract	1.27	1.06—1.53	0.010	1.02	0.82—1.28	0.846
Urinary	1.44	1.20—1.73	<0.001	1.00	0.83—1.19	0.957
Sexual function	1.34	1.15—1.55	<0.001	0.98	0.80—1.20	0.805
Attention/memory	2.15	1.50—3.07	<0.001	1.36	1.02—1.81	0.034
Miscellaneous	1.26	1.11—1.43	0.001	0.99	0.89—1.10	0.825
NMSS total score	0.98	0.90—1.07	0.717	1.04	0.97—1.11	0.274

Adjusted odds ratios (OR) and 95% confidence intervals (CI) from multivariable multinomial logistic regression (MLR) for the odds of having improved or worsened NMS at follow-up associated with baseline measurement of the same NMS. MLR models were adjusted for sex, time to follow-up, disease duration at baseline, and age at baseline. Improvement or worsening of NMS was defined according to the MDC and ''stable'' group was used as reference. Perceptual problems/hallucinations domain was excluded from these analyses due to the low number of subjects showing changes beyond MCD at follow-up. *Abbreviations*: MDC, minimally detectable change; NMS, non-motor symptoms.

Factors associated with minimal detectable change in NMS at follow-up

The minimal detectable change (MDC) establishes the bounds beyond measurement error where a true change in NMS can be detected. Table 2 shows the MCD of NMSS, according to its psychometric attributes. Between 20% and 40% of PD patients experienced a change in NMSS domains beyond MCD at follow-up, except for perceptual problems/hallucinations, where only 3% of the sample had a change of more than three points. Due to the low number of subjects ($\leq$2) in ''improvement'' and ''worsening'' subgroups, this domain was not analyzed further. The domains showing the greatest proportion of converters were mood/apathy and miscellaneous domains ($\approx$40%), followed by Urinary and Sexual function domains ($\approx$35%). Intriguingly, the proportion of subjects with improved or worsened symptoms among those showing changes was comparable.

To test whether sex increased/decreased the odds of NMS modification, MLRs were fitted. Unadjusted MLR analyses revealed that male sex increased the likelihood of sexual symptom worsening at follow-up visit (OR = 9.45, $p = 0.039$). This finding remained significant after adjusting for follow-up time, age at baseline, disease duration at baseline, and initial sexual function NMSS score (OR = 10.1, $p = 0.038$). Contrarily, sex could not significantly predict improvement or worsening of the remaining non-motor domains compared with the group with stable symptoms, neither in univariable nor in multivariable models. Intriguingly, multivariable MLR analyses indicated that higher NMSS sub-scores at baseline were the only predictors significantly associated with symptom improvement at follow-up, after adjusting for sex, time to follow-up, age at baseline, and disease duration at baseline (Table 3). Nonetheless, greater baseline burden in attention/memory and cardiovascular symptoms significantly predicted worsening of symptoms at follow-up, as well. That is, baseline measurements of attention/memory and cardiovascular increased the likelihood of both, improvement and worsening of symptoms, compared to stable group, but the odds ratios for improvement were higher.

Time to follow-up was not a significant predictor for improvement or worsening of any NMS in multivariable MLR models, except for mood/apathy domain. A one-unit increase in time to follow-up (one year increase) increased the odds of mood/anxiety worsening vs. not changing (OR [95% CI] = 1.66 [1.14-2.42], $p = 0.009$). Further adjusting the model for levodopa-LEDD and DA-LEDD confirmed this result (OR [95% CI] = 1.58 [1.06-2.38], $p = 0.027$).

Discussion

In the present study, we evaluated the natural progression of NMS during the disease course of PD with a special focus on sex differences. According to our findings, on average, NMS progressed slowly in both males and females, being gastrointestinal symptoms the ones that worsened significantly over time. However, the inter-individual heterogeneity was high. By more exhaustively assessing the true NMS changes using MCD, we observed that about a quarter of PD patients experienced worsening of NMS. Sex predicted sexual function worsening during the course of the disease in male PD. Moreover, higher baseline NMS scores in attention/memory or cardiovascular domains increased the likelihood of symptom worsening in the future in both males and females, although overall higher initial symptoms were associated with symptom improvement. As far as we know, this is the first study evaluating the natural evolution of NMS by sex in PD patients using NMSS in a Spanish cohort and assessing the progression by minimal detectable change.

Previous studies have already evaluated the presence and progression of NMS in PD.[18,19,24] However, the influence of sex on the progression of NMS in PD has not been explored until recently. Picillo et al.,[20] and Kurlawala et al.[25] analyzed data collected in Parkinson's progression market initiative (PPMI) cohort over a period of 5 and 7 years, respectively. Kurlawala et al.,[25] claimed that sex had a strong influence on NMS progression, but their findings indicate that the rate of progression was similar between male and female PD patients, except for REM sleep behavior disorder and cardiovascular symptoms measured with SCOPA-AUT, both increasing at a faster rate in male PD patients. On the other hand, Picillo et al.,[20] concluded that no sex differences existed in the progression of NMS after controlling for confounding variables. Nonetheless, NMSS questionnaire was not used in PPMI cohort. To the best of our knowledge, the first study reporting the evolution NMS using NMSS using sex perspective was published recently. Chen et al.,[26] performed a retrospective analysis in a Taiwanese cohort showing that the evolution of NMS was similar in male and female PD patients and symptoms progressed slowly. The same year, in an early PD Chinese cohort, Ou et al.,[27] also found that, even though the majority of NMSS domains increased over time, the effect size was small. The results from these studies are completely in line with our present results, where no time or sex effect was observed on NMS progression using LMM.

A novel aspect of this study is that we used the MDC to explore the proportion of PD patients that experienced progression or regression of NMS. Martinez-Martin et al.,[23] proposed some cutoff values based on measurement error of the NMSS. Based on these boundaries, we explored the presence of NMS changes beyond measurement noise to reveal potential factors predicting an actual evolution of NMS. According to our results, male sex was associated with an increased likelihood of sexual function worsening, similar to the findings of Ou et al.[27] However, sex could not predict an improvement or a worsening of NMS beyond MDC in any other domain, suggesting the small effect of sex on NMS evolution. Moreover, we observed that NMS remained within the limits of MDC at follow-up in more than half of the sample. Other authors have also reported that the frequency of NMS remains stable in early-stage PD patients over the course of 2 years.[21] Intriguingly, multivariable MLR showed a significant median reduction of symptoms in those patients with higher initial NMS burden, similar to the results of Prakash et al.[22] A regression to the mean phenomenon could at least partially explain this observation.[28] It is worth mentioning that attention/memory and cardiovascular domains also showed the opposite trend, i.e., greater NMS burden at baseline increased the odds of symptom worsening at follow-up. It is well-known that cognitive impairment tends to progress over the course of PD, but cognitive decline might be more prominent in some subsets of PD patients.[29,30] Cardiovascular symptoms, like orthostatic hypotension, can appear in early phases of PD, but are typically attributed to a later stage.[31] In fact, a common mechanism for autonomic dysfunction and cognitive impairment has been suggested in PD.[32] Although the neural underpinnings of this relationship remain unknown, hypoperfusion of the brain, impaired baroreceptor reflex and alpha-synuclein deposits in peripheral nervous system could contribute.[33] On the other hand, the observation that high attention/memory and cardiovascular symptoms burden could predict both improvement and worsening of symptoms at follow-up highlights the notorious inter-individual heterogeneity. This suggests that the timing, rate, and direction of NMS progression varies widely among individuals with PD, most probably with a non-linear relationship, and identifying clusters of PD patients is of uttermost importance for effective clinical management.

Age and medication are recognized to influence on the manifestation of NMS. Both factors were used as covariates and our study provided consistent results with previous studies. Age was associated with an increased progression of NMS, mainly related to autonomic dysfunction. A cross-sectional study also reported that age was related to erectile dysfunction, urinary symptoms, constipation and orthostatic hypotension.[34] In a similar vein, a recent longitudinal study found that age was a risk factor for an increased burden of NMS.[27] Regarding dopaminergic drugs, previous studies support the notion that NMS lacks association with total LEDD.[6,8,35,36] In this work, we explored how adjustments on dopaminergic drugs affect NMS in terms of longitudinal evolution, confirming that levodopa or DAs do not have an effect on the progression of most NMS, similar to other studies.[19,26] However, we revealed that DA-LEDD was negatively and significantly associated with Mood/Apathy scores, whereas levodopa-LEDD was positively and significantly associated with the same domain. Meta-analytic evidence supports that DAs have a positive effect on the mood and motivational symptoms in PD patients,[37] similar to our findings, and our results provide novel insights into the possible role of levodopa on mood disorders in PD. A study from our group found that increasing the dose of DA therapy was associated with worsening of excessive daytime sleepiness in PD patients at

follow-up visit,[13] but in the current study we did not find such a relationship with Sleep/Fatigue score.

The main limitation of the current study is its retrospective design. Also, sample size might have been insufficient given the large between-subject variability. Moreover, our study sample consisted of Spanish subjects with PD, which limits the generalization of current results to other ethnicities. Nevertheless, in view of comparable findings with Taiwanese and Chinese PD samples in studies with similar designs, we expect that our results could be consistent across ethnic groups. Lastly, we lacked a healthy control group to compare our findings and to establish whether the sex differences that we observed in NMS progression are specific to PD or could be related to ageing. Despite these limitations, our study has several strengths. On one hand, it is the first study evaluating the natural evolution of NMS in PD patients over such a large period using the NMSS in a Spanish population and focusing on sex differences. Such a long follow-up and incorporating sex perspective gives a more rational insight of how NMS progress over time in PD. On the other hand, we used MDC to establish true changes in NMS and to carefully assess the effect of time and baseline measurements while controlling for potential confounders in the analyses.

In conclusion, this study suggests that there is a large inter-individual variability in the observable NMS changes over time in PD patients. NMS symptoms remain stable in about half of PD patients, whereas a quarter shows worsened symptoms. In that sense, sex has an effect on the evolution of genitourinary problems, whereas the remaining NMS progress similarly between male and female PD patients. Higher baseline NMS burden in attention/memory and cardiovascular domains increases the odds of symptom worsening over time. The notion that high initial NMS burden increased the odds of symptom improvement at follow-up visit independently of the follow-up time deserves further assessment in future studies. Given the prevalence of NMS in PD patients and their influence on the quality of life, our findings are relevant for the clinical management of PD patients. Future prospective studies should include larger sample sizes with balanced male and female representation. Finally, reporting results based on minimal clinically important changes in contrast to mean changes may provide a more reliable insight into the diversity of long-term NMS evolution and its potential clinical implication for phenotypic PD characterization. These novel findings complement previous literature on the predication of NMS progression in PD.

Ethical approval

The study protocol was approved by the regional clinical research ethics committee.

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Informed consent

All participants gave written informed consent prior to their participation in the study, in accordance with the tenets of the Declaration of Helsinki.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Availability of data and material

Data are available upon reasonable request.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.nrleng.2025.07.006.

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