Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Prevalence and Incidence of Nonmotor Symptoms in Individuals with and Without Parkinson's Disease

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ABSTRACT: Background: The prevalence ratio (PR) and incidence rate ratio (IRR) of nonmotor symptoms (NMS) were calculated for early Parkinson's disease (PD) versus non-PD from 2 observational studies.

Methods: NMS were assessed through the self-reported Non-Motor Symptom Questionnaire in the online Fox Insight study and through self- and clinician-rated scales in the Parkinson's Progression Marker Initiative (PPMI) study. Age- and sex-adjusted/matched PR and IRR were estimated for each NMS by PD status using Poisson regression.

Results: Most NMS occurred more frequently in PD. Among 15,194 Fox Insight participants, sexual dysfunction had the largest adjusted PR (12.4 [95% CI, 6.9–22.2]) and dysgeusia/hyposmia had the largest adjusted IRR over a 2-year median follow-up (17.0 [95% CI, 7.8–37.1]). Among 607 PPMI participants, anosmia had the largest PR (16.6 [95% CI, 6.1–44.8]). During the 7-year median follow-up, hallucinations had the largest IRR (13.5 [95% CI, 6.3–28.8]).

Conclusion: Although many NMS are more common in early PD than in non-PD, their occurrence may differ with time (hallucinations) or data collection methods (sexual dysfunction).

Nonmotor symptoms (NMS) in Parkinson's disease (PD) are diverse, become increasingly prominent throughout the course of disease, and are major determinants of quality of life and disability.[1,2] Many NMS common in PD are also associated with aging.[3–5] This convergence of age-related changes and PD-associated progression increases the burden of NMS in those living with PD.[6–9]

Patients and caregivers may be unaware that certain NMS are linked to PD, leading to nondeclaration of symptoms.[2,10–12] Therefore, understanding the extent to which NMS are accentuated in patients with PD compared with non-PD age-matched peers could help pinpoint symptoms more specific to disease. These symptoms could also be more amenable to future therapeutic interventions.

We compare the prevalence and incidence of NMS between people with early PD versus non-PD using data from longitudinal and methodologically distinct studies.

Methods

Study Cohorts

Fox Insight (FI) is an online study sponsored by The Michael J. Fox Foundation (MJFF) in 2017 that includes participants with and without self-reported PD.[13] We included those with early PD (≤3 years). Participation is open globally to anyone aged ≥18 years. The informed consent and study protocol are reviewed by the New England Institutional Review Board (IRB).

The Parkinson's Progression Marker Initiative (PPMI) study is an observational, multicenter, in-person study sponsored by MJFF that began enrollment in 2010.[14] People with early, untreated PD (≤2 years diagnosis by a clinician) and healthy controls without PD were matched by age and sex at enrollment. Participants also underwent dopamine transporter imaging.

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Clinical sites were from the United States, Europe, Israel, and Australia. The protocol was approved by the IRB at each center. Participants provided written informed consent.

NMS Measures

FI participants self-report NMS online every 90 days using the Non-Motor Symptom Questionnaire (NMSQ) screening instrument that queries individuals about 30 NMS during the past month.[6] A "yes" response at the first (ie, baseline) visit for an individual symptom was considered a prevalent symptom, and follow-up responses for that symptom were no longer considered. If the particular symptom was not prevalent at the first visit, then the first "yes" response to that individual item was considered a within-study symptom incidence.

In PPMI, 21 NMS assessed by various scales and questionnaires were selected that reasonably corresponded to those symptoms assessed in FI. The Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I includes self- and rater-administered questions. Scores of "slight" to "severe" were considered a "yes" response. The MDS-UPDRS was assessed quarterly for year 1, biannually to study year 5, and annually thereafter. The Scale for Outcomes in Parkinson's Disease–Autonomic (SCOPA-AUT) self-administered questionnaire was used for assessing autonomic NMS.[15] Responses of "sometimes/regularly/often" were "yes" events. The REM Sleep Behavior Disorder Questionnaire (RSDQ) assessed the presence of sleep-related NMS with yes/no responses.[16] The SCOPA-AUT and RSDQ were administered biannually for year 1 and annually thereafter. A University of Pennsylvania Smell Identification Test (UPSIT) score of ≤18 classified people as anosmic at baseline.[17]

Statistical Analysis

For each NMS, counts of incident and prevalent cases were tabulated separately for groups with and without PD; the total length of follow-up times in person-years (PY) were calculated, and raw incidence rates were computed as the following: (no. incident cases/PY) × 1000. Poisson regression models with robust variance generated incidence rate ratios (IRRs) and 95% confidence intervals (CIs) between groups with and without PD for each NMS. For FI, model-derived IRRs and 95% CIs included unadjusted and adjusted (including the offset as log[follow-up time] and all interactions between PD status, sex, and baseline age) estimates. For PPMI, no sex and age adjustments were made because the groups with and without PD were prospectively matched. Bonferroni correction was performed for multiple testing in each cohort. Analyses used R (version 4.0.5) with *lmtest* and *sandwich* packages for Huber–White robust variance estimation. Additional comparisons used χ^2 and unpaired (Welch) *t*-tests for categorical and continuous variables, respectively.

Results

The FI analysis data set included 9814 participants with early PD and 5380 non-PD participants (Figure S1). Compared with the non-PD group, the group with PD in FI were older and had more men (Table 1). PPMI included 416 participants with early de novo PD and 191 non-PD participants, with no differences in age and sex.

The FI population with PD was older and had longer PD durations than the PPMI participants. The FI non-PD population was younger than the PPMI non-PD population. Of the FI population with PD, 80% reported taking symptomatic PD medications at baseline (Table S1), whereas PD medication use was not permitted at enrollment in PPMI.

FI NMS Prevalence and Incidence

In FI, sex- and age-adjusted baseline prevalence ratios (PRs) were significant for 18 NMS, demonstrating a greater prevalence in PD versus non-PD (Fig. 1A, Table S2). Sexual dysfunction had the largest PR, indicating that the proportion of those reporting sexual difficulties at baseline was 12.4-fold higher in PD. Symptoms with CIs including 1 (indicating no difference) were tenesmus, bowel incontinence, delusions, hallucinations, somniloquy, vivid dreams, dizziness, and diplopia.

The median (first quartile, third quartile) duration of follow-up time was 2.0 (1.0, 3.0) years for participants with PD and 2.0 (0.8, 3.0) years for non-PD participants. Incidence rates were consistently higher in the group with PD compared with the non-PD group (Table S3). Adjusted IRRs were significant for 17 NMS (Fig. 1B). The highest adjusted IRR was for dysgeusia/hyposmia. There were no differences for nausea/vomiting, tenesmus, and nocturia.

A sensitivity analysis among those with an earlier PD duration of ≤2 years, such as PPMI (average disease duration, 0.8 ± 1.23 years), had similar PR and IRR estimates (Tables S4 and S5).

PPMI NMS Prevalence and Incidence

In PPMI, baseline PRs were significantly higher in the group with PD for 10 NMS (Fig. 1C, Table S6). Anosmia (via the UPSIT) had the largest PR, with a 16.6-fold greater prevalence in PD than non-PD. Symptoms with CIs including 1 were nocturia, bowel incontinence, hallucinations, insomnia, somniloquy, vivid dreams, and hyperhidrosis.

The median duration of follow-up time was 7.0 (5.1, 7.9) years for PPMI participants with PD and 7.1 (5.0, 8.0) years for non-PD PPMI participants. The IRRs for 18 of the NMS were statistically significant (Fig. 1D, Table S7). The greatest IRR was for rater-assessed hallucinations (IRR, 13.5 [6.3–28.8]). Only nocturia had an IRR CI including 1.

TABLE 1 *Characteristics of the Fox Insight and PPMI cohorts*

	Fox Insight (n = 15,194)			PPMI (n = 607)				
	PD (n = 9814)	Non-PD (n = 5380)	PD vs. non-PD *P* value★	PD (n = 416)	Non-PD (n = 191)	PD vs. Non-PD *P* Value★	Fox Insight PD vs. PPMI PD *P* Value★	Fox Insight Non-PD vs. PPMI Non-PD *P* Value★
Baseline age, years								
Mean (SD)	64.9 (9.7)	57.6 (13.5)	**<0.0001**	62.1 (9.7)	61.6 (11.1)	0.577	**<0.0001**	**<0.0001**
Sex, n (%)								
Male	5243 (53)	1201 (22)	**<0.0001**	272 (65)	123 (64)	0.885	**<0.0001**	**<0.0001**
Female	4571 (47)	4179 (78)		144 (35)	68 (36)			
Race, n (%)								
White	9249 (94)	5036 (94)	0.12[a]	386 (93)	179 (94)	0.805[a]	0.26	0.95
Ethnicity, n (%)								
Non-Hispanic/Latino	9063 (92)	4994 (93)	0.30[b]	407 (98)	189 (99)	0.529[b]	**<0.0001**	**0.0018**
Hispanic/Latino	329 (3)	198 (4)		9 (2)	2 (1)			
Not answered/unknown	422 (4)	188 (3)		0	0			
Years with PD diagnosis								
Mean (SD)	1.4 (1.1)	N/A	N/A	0.5 (0.5)	N/A	N/A	**<0.0001**	N/A

★χ^2 tests were performed for categorical variables, and unpaired (Welch) *t*-tests were performed for continuous variables. Bold text indicates a statistically significant difference with a P value < 0.05.
[a]White vs. all others.
[b]Non-Hispanic/Latino vs. all others.
Abbreviations: PPMI, Parkinson's Progression Marker Initiative; PD, Parkinson's disease; SD, standard deviation; N/A, not applicable.

A sensitivity analysis that shifted the PPMI participants' baseline visit up by ≈9 months to be more aligned with FI disease duration showed similar PR and IRR patterns, but point estimates were generally increased (Tables S8 and S9).

Discussion

We estimated the PRs and IRRs of NMS between participants with and without PD from 2 observational studies with different inclusion criteria, data collection methods, and assessments. Despite these methodological differences, NMS of the upper gastrointestinal tract, bowel and bladder, memory, and mood domains were consistently more common in early PD and throughout follow-up compared with aging without PD. These data reaffirm the extent to which PD accentuates the occurrence of specific NMS beyond aging. It is also apparent that some NMS traditionally associated with mid to later stages of disease are present earlier on (falling, sexual dysfunction, sialorrhea, and dysphagia).[18]

The prevalence of olfactory dysfunction, dysphagia, sialorrhea, urinary urgency, constipation, forgetfulness, apathy, anxiety, and depression were all significantly more common in early PD than in non-PD and are also risk markers for PD.[19] Despite their association with PD risk, some are commonly underreported because the symptom is not recognized by the patient as being PD related.[20,21] Underreporting may also occur due to the lack of self-awareness of the symptom. For instance, anosmia prevalence was higher in PPMI participants with PD than those self-reporting hyposmia/dysgeusia from FI (34.9% vs. 29.1%; $P = 0.011$). Loss of awareness of hyposmia has been linked to cognitive impairment in PD, demonstrating how the emergence of NMS can be complex and interconnected.[22]

There were some differences in prevalence values between study cohorts possibly due to differences in the scales used, such as self-reported sexual dysfunction (PPMI > FI). In FI, the NMSQ asks if it is "difficult to have sex when trying." In PPMI, men were asked specifically about impotence, anejaculation, and erectile dysfunction treatment, and women were asked about atrophic vaginitis and anorgasmia. A barrier to seeking help for sexual dysfunction in people with PD is the belief that it is embarrassing to bring up with healthcare providers.[20] Therefore, perhaps more targeted questions could overcome some embarrassing aspects of broaching this topic. Prevalence differences could also have been attributed to the higher proportions of men in the PPMI than in FI, as sexual dysfunction is more commonly reported in men with PD rather than women with PD.[23,24]

As participants were followed, the experience of some NMS became increasingly prominent in PD. In PPMI, the IRRs for most NMS increased relative to their baseline PRs, perhaps due to disease progression and PD-related medications. For example,

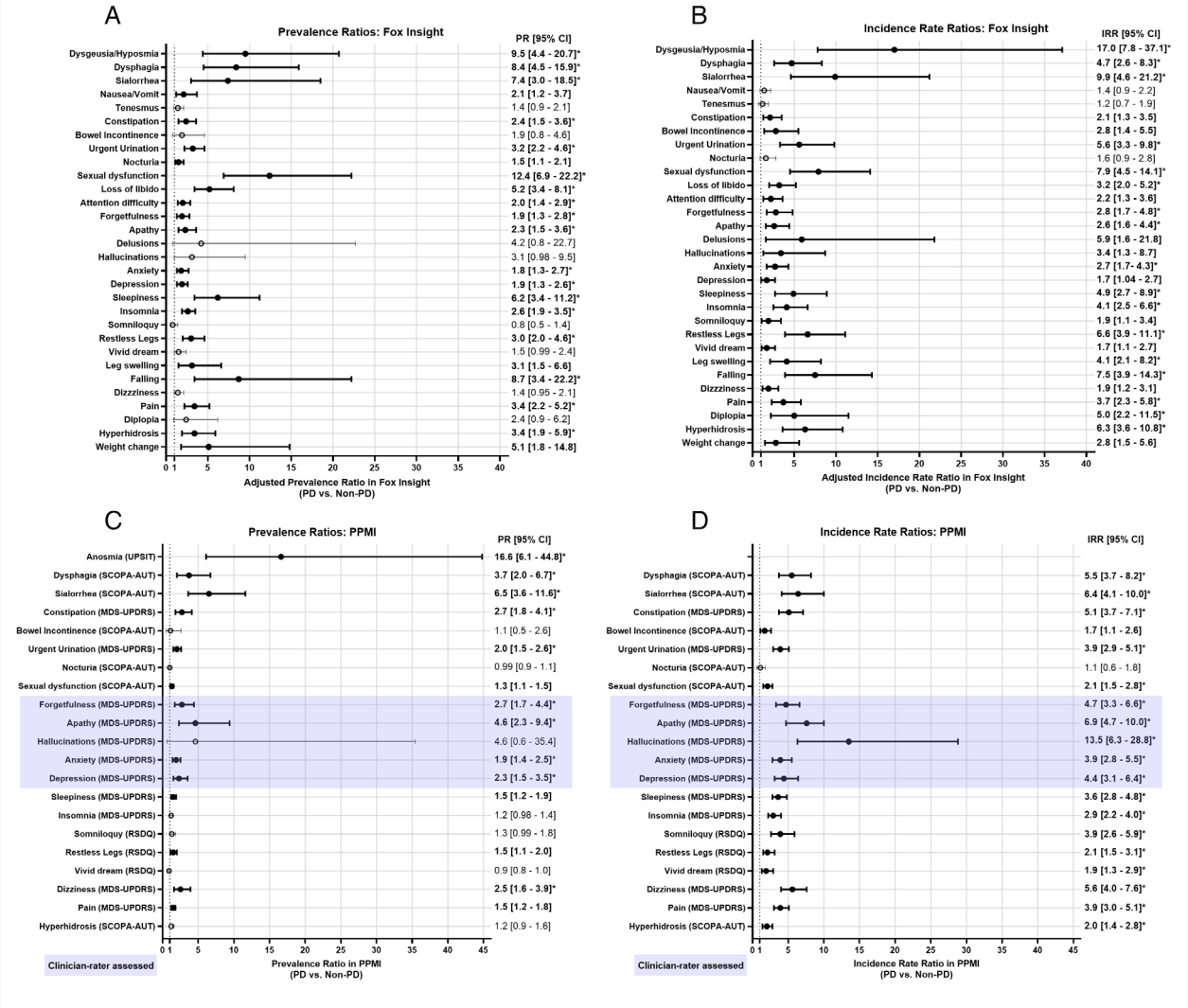

FIG. 1. (**A**) Fox Insight–adjusted PRs, (**B**) Fox Insight–adjusted IRRs, (**C**) PPMI PR, and (**D**) PPMI IRR with 95% CIs of nonmotor symptoms between participants with and without PD. (●) Bold 95% CIs do not cross 1; (○) cross 1. *$P < 0.05$ after Bonferroni correction. CI, confidence interval; IRR, incidence rate ratio; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson's Progression Marker Initiative; PR, prevalence ratio; RSDQ, REM Sleep Behavior Disorder Questionnaire; SCOPA-AUT, Scale for Outcomes in Parkinson's Disease–Autonomic; UPSIT, University of Pennsylvania Smell Identification Test.

the emergence of hallucinations over time was dramatic in the PPMI population with PD. Development of hallucinations in PD increases with the use of anti-PD medications.[25,26] It is also important to consider that dopaminergic treatments may improve rather than exacerbate NMS (eg, depression, apathy, pain), which likely contributed to earlier disparities in symptom occurrences between studies.[27]

There are some limitations to our study. First, we could not match all symptoms between cohorts. For those symptoms that were matched, differences exist because the NMSQ is a broad patient-reported checklist of symptoms, whereas the PPMI scales were a mixture of clinician assessments and patient-reported questionnaires. Second, because the FI and PPMI studies enrolled individuals with a prior diagnosis of PD, it was impossible to determine the exact timing of the emergence of NMS relative to disease onset. Thus, our estimated incident rates can only be considered within-study incident rates. Third, the time scales for recalling symptoms were different between the assessment scales, contributing to issues of subjective recall. Lastly, we did not assess the severity of symptoms in relation to their occurrence. Therefore, we cannot determine which NMS contributed most to disease burden and when they are actually most impactful, as previously reported.[28–31]

This report provides a comprehensive summary of the differences in the occurrence of NMS between people with and without PD. We show that the prevalence and emergence of many NMS in PD are greater than expected from aging alone. These symptoms are likely caused by underlying disease processes as

well as the medications used to treat the motor aspects of PD.[32] Therapies are available for treating some of these NMS, which can improve the quality of life;[33] however, barriers to reporting these symptoms exist, and better therapies are still needed.[34,35]

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

M.P.: 1B, 1C, 2A, 2C, 3A
K.H.: 1C, 2A, 2B, 2C, 3B
K.K.: 1B, 2A, 2C, 3B
C.S.V.: 1A, 1B, 1C, 2A, 2C, 3A, 3B

Disclosures

Ethical Compliance Statement: Fox Insight participants provided informed e-consent through the Fox Insight website. The Fox Insight informed consent and study protocol are reviewed by the New England Institutional Review Board (IRB; IRB no. 120160179, Legacy IRB no. 14–236). The Parkinson's Progression Marker Initiative (PPMI) protocol was reviewed and approved by the IRB at each center. Written informed consent was obtained from all PPMI participants. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The data supporting the findings of this study are available at the Fox Den website (https://foxden.michaeljfox.org/insight/explore/insight.jsp) and the Parkinson's Progression Markers Initiative website (https://www.ppmi-info.org/) ■

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Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Fox Insight participant flowchart.

Table S1. Parkinson's disease medication use at first visit among the Fox Insight Parkinson's disease group.

Table S2. Baseline prevalence and adjusted prevalence ratios from Fox Insight.

Table S3. Incidence and adjusted incidence rate ratios from Fox Insight.

Table S4. Baseline prevalence and adjusted prevalence ratios from Fox Insight with Parkinson's disease duration ≤2 years.

Table S5. Incidence and adjusted incidence rate ratios from Fox Insight with Parkinson's disease duration ≤2 years.

Table S6. Baseline prevalence and prevalence ratios from Parkinson's Progression Marker Initiative.

Table S7. Incidence and incidence rate ratios from Parkinson's Progression Marker Initiative.

Table S8. Baseline prevalence and prevalence ratios from Parkinson's Progression Marker Initiative with visit 3 as baseline.

Table S9. Incidence and incidence rate ratios from Parkinson's Progression Marker Initiative with visit 3 as baseline.

Appendix S1. Supplemental methods: sample criteria.