Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Demographic Influences on the Relationship Between Fatigue and Quality of Life in Parkinson's Disease

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Abstract: Background: Fatigue has a major impact on health-related quality of life (HR-QOL) in Parkinson's disease (PD).

Objectives: To determine whether demographic characteristics modify the relationship between fatigue and HR-QOL.

Methods: Patients with PD in the Fox Insight study completed the Parkinson Fatigue Scale (PFS-16) and Geriatric Depression Scale (GDS-15). Linear regression examined the relationship between the PFS-16 and Parkinson Disease Quality of Life, as modified by age, sex, and GDS-15.

Results: A total of 1029 participants (44% female, mean age 67.4 years, and mean disease duration 4.6 years) were included in this analysis. Multivariable regression modeling demonstrated a negative effect modification for age ($\beta = -0.07$, $P < 0.001$) and a positive effect modification for the GDS-15 ($\beta = 0.057$, $P = 0.002$), but not for sex ($\beta = -0.021$, $P = 0.231$).

Conclusion: The association between fatigue and worse HR-QOL is greater at younger ages and in individuals with more depressive symptoms. Targeted therapeutics for these individuals may provide the greatest impact on fatigue in PD.

Parkinson's disease (PD), which affects nearly 1 million people in the United States,[1] has a wide range of motor and nonmotor manifestations. Fatigue, 1 of the most common nonmotor symptoms in PD, occurs in up to 70% of patients[2] and is associated with lower health-related quality of life (HR-QOL)[3] and an increased risk of disease complications.[4] In comparison with other PD symptoms, fatigue comprises multiple dimensions[5,6] and is poorly responsive to pharmacological and nonpharmacological intervention,[7] making it 1 of the most challenging aspects of the disease to manage.[8,9] Given the breadth of this problem, understanding the risk factors for PD fatigue and its effects on HR-QOL is critical in this patient population.

Specifically, both age and sex have strong influences on the manifestations of PD,[10,11] but their relationship to fatigue in PD are not well understood. Some studies indicate that fatigue is more common in women with PD compared with men,[3,4] but sex differences on severity and impact of fatigue are limited. As for age, both older[12] and younger[13] age have been reported as risk factors for PD fatigue. This study was undertaken to understand the relationship between PD fatigue and age and sex and to investigate whether age and sex modify the relationship between PD fatigue and HR-QOL.

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Methods

Sample

The sample for this analysis consisted of a subset of individuals with self-reported PD participating in the Fox Insight study. Study methodology for Fox Insight has been reported elsewhere in detail.[14,15] Briefly, Fox Insight is an online-only longitudinal observational study in which individuals with self-reported PD participate in study activities via an online platform. Study activities include questionnaires, deployed via a predefined schedule of activities, regarding demographics, motor and nonmotor symptoms of PD, quality of life, exercise habits, environmental risk factors for PD, and others. In additionally, substudies on topics of interest to the investigators can be launched ad hoc via email invitations to participants.

Participants in the PD cohort of the Fox Insight study were invited to participate in this substudy on fatigue in PD[5] if they met the following criteria: provided data on their age, sex, year of diagnosis, and completed the Fox Insight assessments regarding depression (15-item Geriatric Depression Scale [GDS-15]) and Physical Activity Scale for the Elderly (PASE) within the prior 90 days. This latter requirement was necessitated by other study objectives not considered here.

Assessments

Global assessments administered as part of study activities in Fox Insight[14] and considered in this analysis include the following: (1) demographics (age, sex, year of diagnosis); (2) medications (self-reported use of levodopa, dopamine agonist, or other PD medications); (3) the Parkinson's Disease Quality of Life–8 item (PDQ-8[16]; this is an 8-item questionnaire with higher scores indicating worse quality of life)—the PDQ-8 single index (PDQ-8-SI) score was calculated as follows: (sum of scores of each question)/(4 [maximum score per question] × 8 [total number of questions]) × 100; (4) the GDS-15[17] (higher scores indicate more severe depression); and (5) the Movement Disorders Society Unified Parkinson's Disease Rating Scale Part II (MDS-UPDRS-II),[18] a 13-item scale that asks about difficulty participating in activities of daily living (higher scores indicate more difficulty).

In addition, the Parkinson's Fatigue Scale (PFS-16)[19] was deployed for purposes of this study. This is a 16-item scale that assesses symptoms of fatigue in the prior 2 weeks. Higher scores indicate more severe fatigue.

Analysis

Descriptive statistics were used to summarize basic demographics and questionnaire scores. Spearman correlation coefficients examined univariable relationships between PFS-16 and PDQ-8 with demographics, GDS-15, and MDS-UPDRS-II.

Multivariable linear regression was used to examine the relationship between PFS-16 and HR-QOL. Covariates included established contributors to HR-QOL in PD, namely, disease duration and, as a measure of motor disease severity, MDS-UPDRS-II. Interaction terms between PFS-16 and age and sex were separately introduced into the model to examine effect modification. Given the potential mediating effect of depression on the relationship between fatigue and HR-QOL,[20] it was included as a covariate, and a separate model examined it as an effect modifier by including an interaction term between PFS-16 and GDS-15.

Results

Email invitations for this study were sent in March and May 2019 to 3531 eligible Fox Insight participants; 1036 responded to the email (response rate, 29.3%) and completed the PFS. Compared with the respondents, nonrespondents had longer disease durations (mean [standard deviation, SD] 5.3 [5.7] vs. 4.6 [5.3]; $P = 0.0002$] but did not differ significantly in age, sex, education, or GDS-15 scores. A total of 7 respondents were excluded as a result of missing data in global Fox Insight assessments; thus, the final sample included in this analysis was 1029 participants. Sample demographics, disease characteristics, and measures of fatigue, depression, disease severity, and HR-QOL are shown in the online supplement as are univariate correlation between variables.

Multivariable models investigating the relationships between fatigue and HR-QOL are shown in Table 1. Fatigue (higher PFS-16 score) was associated with worse PDQ-8-SI score independent of age, disease duration, MDS-UPDRS-II, and GDS-15 scores. There were significant interactions between PFS-16 and age and between PFS and GDS-15 scores. Specifically, as Fig. 1A shows, the effect of PFS-16 on PDQ-8 is greater at younger ages, where the predicted PDQ-8-SI is much higher (worse HR-QOL) with higher levels of fatigue. For older participants, the predicted PDQ-8-SI is much more similar across the range of fatigue severity than for younger participants. By contrast, the effect of PFS-16 on PDQ-8 strengthens for higher GDS-15 scores (Fig. 1B). For higher GDS-15 scores, the predicted PDQ-8-SI increases more dramatically across the range of PFS-16 scores.

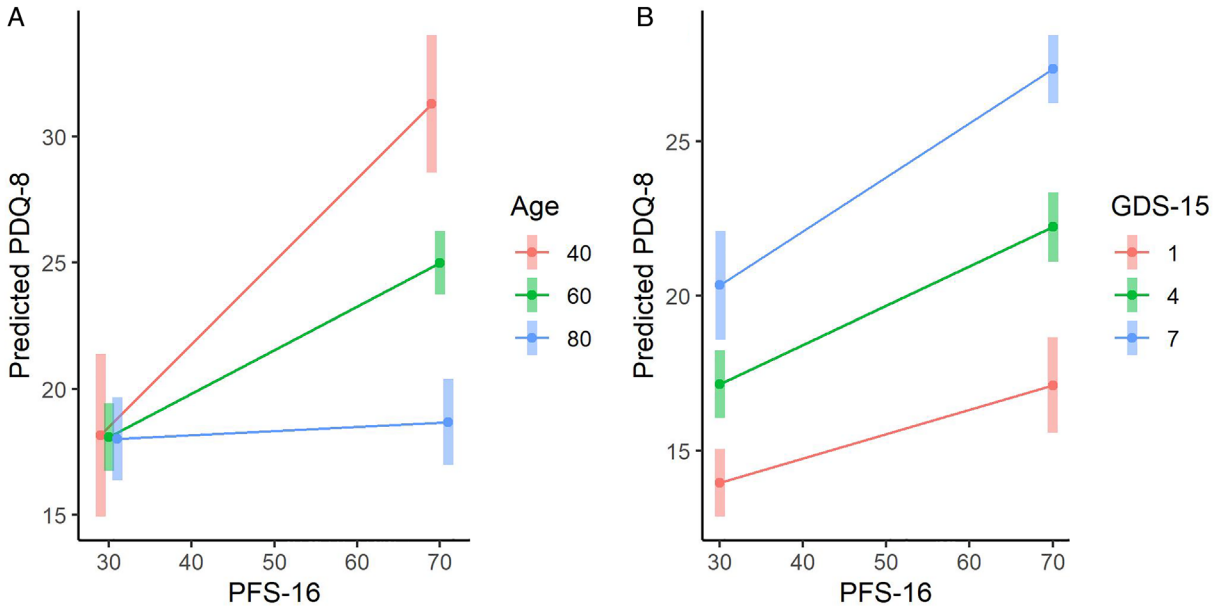
Discussion

This analysis examines the complex interactions between fatigue, depression, and demographic factors on quality of life in a large cohort of individuals with PD. Our results are in agreement with extensive prior literature describing the association between fatigue and poorer HR-QOL in PD.[21,22] This relationship was maintained in our sample after adjusting for a number of confounders. Furthermore, our results indicate that the relationship between fatigue and HR-QOL differs by age and depressive symptoms. That is, the association between fatigue and worse HR-QOL is greater at younger ages and in individuals with more depressive symptoms. This is consistent with other work

TABLE 1 *Multivariable relationship with quality of life (PDQ-8-SI)*

Model Variable	β Coefficient	95% CI	Standardized β Coefficient	Standardized 95% CI	*P* Value*	Model *P* Value	Model-Adjusted R^2
Base model							
Intercept	6.88	1.988–11.772	0	−0.035 to 0.035	0.006	<0.001	0.680
Female sex	1.034	−0.153 to 2.221	0.03	−0.005 to 0.065	0.088		
Age	−0.177	−0.242 to −0.112	−0.098	−0.134 to −0.062	<0.001		
Disease duration	0.044	−0.076 to 0.164	0.014	−0.024 to 0.052	0.469		
MDS-UPDRS-II	1.096	1.002–1.19	0.522	0.477–0.567	<0.001		
GDS-15	1.482	1.284–1.68	0.329	0.285–0.372	<0.001		
PFS	0.116	0.071–0.161	0.112	0.069–0.155	<0.001		
Effect modification by age							
Intercept	−20.565	−35.343 to −5.787	−0.007	−0.042 to 0.027	0.006	<0.001	0.684
Female sex	1.152	−0.029 to 2.333	0.034	−0.001 to 0.069	0.056		
Age	0.23	0.014–0.446	−0.083	−0.119 to −0.047	0.037		
Disease duration	0.048	−0.072 to 0.168	0.015	−0.022 to 0.052	0.432		
MDS-UPDRS-II	1.09	0.996–1.184	0.519	0.475–0.564	<0.001		
GDS-15	1.47	1.274–1.666	0.326	0.282–0.369	<0.001		
PFS-16	0.64	0.369–0.911	0.11	0.068–0.153	<0.001		
Age × PFS-16[a]	−0.008	−0.012 to −0.004	−0.07	−0.105 to −0.034	<0.001		
Effect modification by sex							
Intercept	5.835	0.653–11.017	0	−0.035 to 0.035	0.027	<0.001	0.68
Female sex	3.216	−0.546 to 6.978	0.03	−0.005 to 0.065	0.094		
Age	−0.175	−0.24 to −0.11	−0.097	−0.133 to −0.061	<0.001		
Disease duration	0.039	−0.083 to 0.161	0.012	−0.025 to 0.05	0.522		
MDS-UPDRS-II	1.098	1.004–1.192	0.523	0.478–0.568	<0.001		
GDS-15	1.475	1.277–1.673	0.327	0.283–0.371	<0.001		
PFS-16	0.136	0.081–0.191	0.112	0.069–0.155	<0.001		
Sex × PFS-16[a]	−0.045	−0.118 to 0.028	−0.021	−0.056 to 0.014	0.231		
Effect modification by depressive symptoms							
Intercept	9.105	4.044–14.166	−0.03	−0.069 to 0.009	<0.001	<0.001	0.683
Female sex	1.095	−0.088 to 2.278	0.032	−0.003 to 0.067	0.07		
Age	−0.17	−0.235 to −0.105	−0.094	−0.13 to −0.059	<0.001		
Disease duration	0.046	−0.074 to 0.166	0.014	−0.023 to 0.052	0.453		
MDS-UPDRS-II	1.088	0.994–1.182	0.518	0.473–0.563	<0.001		
GDS-15	0.584	−0.005 to 1.173	0.302	0.256–0.349	0.052		
PFS-16	0.063	0.008–0.118	0.125	0.082–0.168	0.026		
GDS-15 × PFS-16[a]	0.016	0.006–0.026	0.057	0.022–0.093	0.002		

[a]Interaction terms.
*P values are for unstandardized β coefficients.
Abbreviations: PDQ-8-SI, Parkinson's Disease Quality of Life–8 item single index; CI, confidence interval; MDS-UPDRS-II, Movement Disorders Society Unified Parkinson's Disease Rating Scale Part II; GDS-15, Geriatric Depression Scale–15 item.



Age	PFS-16	Predicted PDQ-8 (95% CI)
40	30	18.2 (14.9-21.4)
60	30	18.1 (16.7-19.4)
80	30	18 (16.4-19.7)
40	70	31.3 (28.6-34)
60	70	25 (23.7-26.2)
80	70	18.7 (17-20.4)

GDS-15	PFS-16	Predicted PDQ-8 (95% CI)
1	30	14 (12.9-15.1)
4	30	17.2 (16.1-18.2)
7	30	20.3 (18.6-22.1)
1	70	17.1 (15.6-18.7)
4	70	22.2 (21.1-23.4)
7	70	27.3 (26.2-28.4)

FIG. 1. Plots of predicted PDQ-8 against PFS-16. Values based on models depicted in Table 1: (**A**) interaction between age and PFS-16 and (**B**) interaction between GDS-15 and PFS-16. CI, confidence interval; GDS-15, Geriatric Depression Scale–15 item; PDQ-8, Parkinson's Disease Quality of Life–8 item; PFS-16, Parkinson Fatigue Scale–16 item.

suggesting that younger individuals with chronic disease may be more impacted by fatigue than older individuals,[13] perhaps reflecting differential activities of daily living (eg, ongoing employment outside the home or caring for dependent family members themselves), different expectations for function, or greater uncertainty regarding deviation from an expected life trajectory.[23] The strong and possibly bidirectional relationship between depression and fatigue in PD is well described[24]; our work suggests that the impact on HR-QOL of the co-occurrence of these 2 nonmotor symptoms is multiplicative rather than simply additive.

By contrast, in our cohort, sex and disease duration were not significant predictors of the relationship between fatigue and quality of life. That is, although female sex[25] and disease duration[26] are independently correlated with worse HR-QOL in PD in our and other cohorts, this association does not appear to be affected by levels of fatigue. To our knowledge, this is the first quantification of the interaction between demographic factors, fatigue, depression, and HR-QOL in PD. Given the high prevalence of fatigue in PD, this further underscores the need for effective therapeutics, perhaps particularly targeted at younger or depressed individuals who may benefit the most.

Our study had several notable strengths, including a large sample size, exceeding that of any previous study that analyzed the relationship between fatigue and quality of life in patients with PD. This allows for more precise estimates of associations and allows us to examine the experience of fatigue within subgroups, broadening our understanding of the experience and impact of fatigue across populations. For instance, women with PD, who have traditionally been underrepresented in research, formed nearly half our sample. Interestingly, with this large sample of women and men with PD, we found that sex was not a significant predictor of fatigue scores, either directly or through effect modification. This intriguing difference between our results and the results of other studies[25,27] that recruited smaller proportions of women warrants further study. In addition, our own prior work analyzing free-text responses from the same cohort[5] found that women were more likely to describe fatigue as

overwhelming than men. These apparent contradictions may reflect aspects of fatigue and/or quality of life that are differently captured in quantitative scales such as the PFS-16 or PDQ-8 compared with free-text responses.[28]

The online, community-based nature of Fox Insight enables researchers to bypass traditional recruitment barriers,[29] particularly for individuals for whom transportation to a specialist center is challenging. Nevertheless, some important limitations must be noted. Similar to other research cohorts in PD, participants in Fox Insight are highly educated[15] and may not be representative of the population at large. In particular, the validity of patient-reported outcome measures such as the GDS-15 and PFS-16 are dependent on respondent's cognitive status, which could not be independently verified. Moreover, participants are self-identified as having PD, without independent verification by a movement disorders specialist. However, the demographics and prevalence of motor and nonmotor signs and symptoms of the Fox Insight PD cohort are similar to those of cohorts assessed in person,[15] and concordance between self-reported PD diagnosis in Fox Insight and clinician diagnosis as assessed via virtual visits is high,[30] suggesting external validity for an online-only approach. Nevertheless, objective measures of motor and nonmotor function, which could also have an impact on HR-QOL, are not captured in Fox Insight and therefore could not be accounted for in our models.

Fatigue is a multidimensional symptom of PD with a prominent impact on quality of life and perceived disability. This analysis provides evidence of complex effects between demographic features (age and sex), fatigue scores, and HR-QOL in a large cohort of people with PD. In particular, targeted therapeutics aimed at younger or depressed individuals with PD may provide the greatest impact on fatigue burden, with the important caveat that the drivers of fatigue among these individuals may be different from the drivers of fatigue among older individuals with PD. As the longitudinal data in Fox Insight grows, better assessment of fatigue progression, and potentially the impact of therapeutics, across these individuals will also be possible.

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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.

S.M.: 1B, 1C, 2A, 2B, 2C, 3A, 3B
L.M.C.: 1A, 2A, 2C, 3B
K.N.: 2B, 2C, 3B
R.F.: 2B
A.A.: 2B
B.T.: 2B
S.M.A.: 2C
C.K.: 1A, 1B, 3B
C.M.: 1A, 1B, 1C, 2C, 3B

Disclosures

Ethical Compliance Statement: This study was performed in accordance with the Declaration of Helsinki. This study is approved by the New England Institutional Review Board, and online informed consent is obtained from each participant at enrollment. 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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Supporting Information

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

Table S1. Cohort characteristics and measures of fatigue, quality of life, depression, and activities of daily living

Table S2. Correlations between Parkinson Fatigue Scale scores and demographic characteristics, depression, disease severity, and quality of life.