The impact of fatigue on daily activity in patients with Parkinson's disease

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Chapter 2

Impact of fatigue on health-related quality of life in patients with Parkinson's disease: a prospective study

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Abstract

Objective To investigate the longitudinal association between the impact of fatigue and health-related quality of life and to determine if potential confounders distorted this association.

Design Baseline, 3-, 6- and 12-week assessments of a randomized clinical trial were used.

Setting Outpatient rehabilitation center.

Subjects Patients with idiopathic Parkinson's disease.

Methods Quality of life was assessed with the Parkinson's disease Questionnaire-39 and the Multidimensional Fatigue Inventory was used to assess fatigue. Time-independent and time-dependent factors were investigated for their bivariate association with quality of life by applying random coefficient analysis. Candidate confounders were successively added to the longitudinal association model to determine if the relationship between quality of life and fatigue was distorted. A change beyond 15% of found regression coefficient of the Multidimensional Fatigue Inventory was considered significant.

Results One hundred and fifty-three patients were included. Impact of fatigue was significantly associated with poorer quality of life ($\beta = 0.24$, 95% confidence interval = 0.18 to 0.30). This association was significantly distorted by depression (30.0%) and anxiety (24.1%). No distortion was found for other factors. After controlling for confounders, fatigue remained significantly associated with quality of life ($\beta = 0.12$, 95% confidence interval = 0.06 to 0.18, $r^2 = 2.3\%$).

Conclusions Our results suggest that patients who experience fatigue tend to report lower levels of quality of life. However, this longitudinal relationship is confounded by depression and anxiety and suggests that the unique contribution of fatigue to overall quality of life is rather small.

Introduction

Fatigue is common in patients with idiopathic Parkinson's disease, with prevalence rates ranging from 32% to 50% [1, 2]. However, the lack of a widely accepted definition for fatigue [3] makes it difficult to investigate the impact of fatigue on disease-specific health-related quality of life (HRQOL).

Previous research [4] that used the unidimensional Fatigue Severity Scale to assess fatigue, found significant correlations (Spearman's r) with overall HRQOL and with most domains of HRQOL measured with the Parkinson's disease Questionnaire-39 (PDQ-39). However, another study that controlled for neuropsychiatric symptoms showed that fatigue was only significantly associated with the PDQ-39 domains activities of daily living and cognitions [5].

Havlikova and colleagues [6] used the Multidimensional Fatigue Inventory to investigate the impact of fatigue on HRQOL (PDQ-39). Multivariate analysis showed that different dimensions of fatigue were significantly associated with different domains of HRQOL. Unfortunately, the authors did not control for depression, whereas previous research suggested that depression is a confounder in the relationship between fatigue and physical activity [7] and may therefore be a potential confounder in the association between fatigue and HRQOL.

Thus far, studies that investigated the impact of fatigue on HRQOL have focused on the cross-sectional association between fatigue and HRQOL. However, as fatigue fluctuates in time, associations between fatigue and other demographic and clinical factors may be more accurately reflected using longitudinal study designs with repeated measures in time [8]. Furthermore, longitudinal statistical models take into account the between- and within-subject variance in the association between fatigue and other demographic and clinical factors.

The aim of the present study was to investigate the longitudinal association between impact of fatigue and disease-specific HRQOL. We hypothesized that impact of fatigue, measured with the Multidimensional Fatigue Inventory total score, is significantly associated with poorer overall HRQOL assessed with the PDQ-39 summary index. In addition, we expected that physical fatigue (i.e. Multidimensional Fatigue Inventory physical fatigue subscale) is associated most strongly with physical aspects of HRQOL (i.e. PDQ-39 mobility), whereas mental fatigue (i.e. Multidimensional Fatigue Inventory mental fatigue subscale) is most strongly correlated with cognitive aspects of HRQOL (i.e. PDQ-39 cognitions). Subsequently, we investigated whether these identified

longitudinal associations were significantly distorted by potential confounders such as age [6], gender [6], social support, disease duration [6, 9], disease severity [6, 9], motor impairment [9], cognition, anxiety [9], depression [9] and medication intake.

Methods

The data presented in this study were collected in a prospective randomized clinical trial (the 'Rescue' trial (Rehabilitation in Parkinson's Disease: Strategies for Cueing) QLK6-CT-2001-00120) about the effects of cueing training on gait and gait-related activity in patients with Parkinson's disease [10]. Further details about the design and outcomes of the study have been published previously [10].

Patients were recruited according to the following criteria: 1) age 18-80; 2) diagnosis of Parkinson's disease, defined by the UK Brain Bank Criteria [11]; 3) Hoehn and Yahr stage II-IV [12]; 4) stable drug usage and 5) mild to severe gait disturbance (score > 1 on the Unified Parkinson's Disease Rating Scale item 29) [13]. Patients were excluded if they had: 1) undergone deep brain stimulation or other stereotactic neurosurgery; 2) cognitive impairment (Mini Mental State Examination) < 24) [14]; 3) disorders interfering with participation in cueing training, including neurological (stroke, multiple sclerosis, brain tumor), cardiopulmonary (chronic obstructive disorders, angina pectoris) and orthopedic (osteoarthritis, rheumatoid arthritis and back pain) conditions; 4) unpredictable and long-lasting 'off' periods (score 1 on item 37 and score > 2 on item 39 of the Unified Parkinson's Disease Rating Scale) [13] or 5) had participated in a physiotherapy program two months before starting the trial.

Disease-specific HRQOL was assessed with the PDQ-39 [15]. The PDQ-39 is a self-report questionnaire that consists of 39 items. A summary index and separate scores for eight domains (i.e. mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognitions (4 items), communication (3 items) and bodily discomfort (3 items)) are calculated. Scores are standardized from 0 (best HRQOL) to 100 (worst HRQOL) [15].

Fatigue was assessed with the Multidimensional Fatigue Inventory [16]. The Multidimensional Fatigue Inventory is a reliable and valid self-report questionnaire to measure the multidimensional aspects of fatigue in patients with Parkinson's disease [17]. The Multidimensional Fatigue Inventory assesses the impact of fatigue on daily life and comprises five dimensions (general fatigue, physical fatigue, reduced activity, mental fatigue and reduced motivation). Each subscale contains four items and the obtainable score within each subscale ranges from 4 (absence of fatigue) to

20 (maximum fatigue). A total summed score of all 20 items is recommended to obtain a global indication of fatigue [17].

To establish whether the longitudinal association between the impact of fatigue and HRQOL was distorted, various time-independent and time-dependent variables were measured. The selection of possible confounding factors was based on clinical expertise and previous research. Time-independent variables were treatment allocation [10], age [6], gender [6], social support, disease duration [6, 9], disease severity [6, 9], cognitive functioning and medication intake. Disease severity was assessed with the Hoehn and Yahr scale [12]; cognitive functioning was assessed with the Brixton Test [18] and the Mini Mental State Examination [14].

Time-dependent variables were motor impairment [9], anxiety [9] and depression [9]. Motor impairment was assessed with the Unified Parkinson's Disease Rating Scale part III [13]. The Hospital Anxiety and Depression Scale was used to assess anxiety and depression [19, 20].

All variables were assessed at baseline. The time-dependent variables were also measured at week 3, 6 and 12. One observer from each center, blinded to treatment allocation and not involved in data analysis, performed all assessments in the patients' homes. Each patient was assessed in the on phase, approximately 1 hour after medication intake.

The longitudinal association between the impact of fatigue and HRQOL was evaluated by means of random coefficient analysis [21] (MLwiN version 2.25, Multilevel Models Project Institute of Education, London, UK). In this two-level hierarchical model, repeated measurements are nested within subjects. Based on distribution by visual plot, linear multilevel models were applied.

First, bivariate longitudinal regression analysis was conducted with the PDQ-39 summary index and all eight domains of PDQ-39 separately as dependent variables, and the candidate determinants, including the Multidimensional Fatigue Inventory total score as well as the five different dimensions as independent variables. The found regression coefficients between PDQ-39 and the Multidimensional Fatigue Inventory were recalculated to standardized regression coefficients. Subsequently, regression coefficients were adjusted for treatment allocation. Candidate confounders were successively added to the longitudinal association model to determine if the β-value between PDQ-39 and the Multidimensional Fatigue Inventory was significantly influenced after controlling for time-independent and time-dependent covariates. If

the regression coefficient of fatigue changed more than 15% after controlling for the added variable, the added covariate was considered a potential confounder. If the relationship between PDQ-39 and the Multidimensional Fatigue Inventory was still significant after controlling for the confounder of interest, new candidate confounders were added to the model. The restricted likelihood ratio test was used for allowing random coefficients in the model and to compare the fit of models. A two-tailed significance level of 0.05 was used for all tests.

Results

Table 2.1 presents the characteristics of the 153 included patients.

One patient dropped out three weeks after randomization because of a necessary change of drug treatment. All dependent variables were normally distributed by visual plot.

Bivariate random coefficient analysis between HRQOL and determinants

Table 2.2 shows that the Multidimensional Fatigue Inventory total score and all dimensions of the Multidimensional Fatigue Inventory were significantly associated with the PDQ-39 summary index. Physical fatigue was most strongly associated with physical aspects of HRQOL and mental fatigue showed the strongest association with the cognitive domain of HRQOL.

Confounding factors between HRQOL and fatigue

Table 2.3 presents the adjusted regression coefficient between the PDQ-39 summary index and the Multidimensional Fatigue Inventory total score after correcting for the candidate confounders. The adjustment for treatment allocation did not change the regression coefficient between the PDQ-39 summary index and the Multidimensional Fatigue Inventory total score. Adding depression to the model (Hospital Anxiety and Depression Scale) resulted in a decrease of 30.0% in the regression coefficient of the Multidimensional Fatigue Inventory total score. Controlling for anxiety (Hospital Anxiety and Depression Scale) reduced 24.1% of the found regression coefficient. No significant distortion beyond the 15% increase or decrease was found for treatment allocation, age, gender, social support, disease duration, disease severity, motor impairment, cognition and medication intake.

Table 2.1 Patient characteristics at baseline (N = 153)

	Mean (SD)
Demography	
Age (years)	67.06 (7.54)
Male/female[a]	88/65
Partnered[a]	123
Disease characteristics	
Disease duration (years)	8.25 (5.09)
H&Y (on)	2.78 (0.60)
H&Y II/III/IV (on)[a]	71/64/18
Clinical data	
Early intervention group[a]	76
Late intervention group[a]	77
UPDRS-total (on)	56.03 (16.01)
UPDRS I (on)	3.30 (1.72)
UPDRS II (on)	16.42 (6.03)
UPDRS III (on)	33.05 (11.28)
UPDRS IV (on)	3.34 (3.26)
PDQ-39 summary index	35.43 (13.23)
PDQ-39 mobility	49.68 (23.38)
PDQ-39 activities of daily living	49.16 (24.08)
PDQ-39 emotional well-being	32.57 (19.64)
PDQ-39 stigma	31.29 (23.01)
PDQ-39 social support	13.43 (16.56)
PDQ-39 cognitions	33.82 (19.16)
PDQ-39 communication	29.85 (20.91)
PDQ-39 bodily discomfort	43.63 (24.20)
MFI-total	62.74 (17.94)
MFI general fatigue	13.83 (4.30)
MFI physical fatigue	13.93 (4.51)
MFI reduced activity	13.45 (4.98)
MFI mental fatigue	10.36 (4.68)
MFI reduced motivation	11.16 (4.30)
HADS anxiety	6.90 (3.91)
HADS depression	7.20 (3.50)
Brixton R	22.17 (10.12)
Brixton S	3.99 (2.22)
MMSE	28.17 (1.82)
Levodopa (mg)	457.82 (341.14)
Dopamine agonist[a]	105
Selegeline[a]	22
Levodopa + Entacapone[a]	37
Medication other[a]	46

[a]*Expressed as number of patients*

Table 2.2 Bivariate associations between health-related quality of life and candidate determinants (N = 153)

Determinant	Standardized β value PDQ-39								
	Summary index	Mobility	Activities of daily living	Emotional well-being	Stigma	Social support	Cognitions	Communication	Bodily discomfort
Demography									
Age	0.06	0.16[a]	0.04	0.01	-0.02	0.00	0.11	0.01	-0.04
Gender	-0.08	-0.19[a]	0.00	-0.16[a]	-0.13	-0.05	0.16[a]	0.18[a]	-0.19[a]
Social support	-0.03	-0.13	0.02	-0.06	-0.06	-0.07	0.05	0.13	-0.04
Disease characteristics									
Disease duration	0.32[a]	0.22[a]	0.23[a]	0.10	0.30[a]	0.16[a]	0.19[a]	0.29[a]	0.13
H&Y (on)	0.42[a]	0.48[a]	0.34[a]	0.24[a]	0.22[a]	0.17[a]	0.21[a]	0.25[a]	0.22[a]
Clinical data									
Treatment allocation	0.05	0.07	-0.01	0.01	0.05	-0.01	-0.05	0.02	0.14[a]
UPDRS III (on)	0.18[a]	0.25[a]	0.18[a]	0.10[a]	0.11[a]	0.09	0.03	0.13[a]	0.06
MFI-total	0.30[a]	0.30[a]	0.21[a]	0.27[a]	0.15[a]	0.21[a]	0.26[a]	0.09[a]	0.17[a]
MFI general fatigue	0.24[a]	0.18[a]	0.11[a]	0.19[a]	0.14[a]	0.18[a]	0.15[a]	0.09[a]	0.21[a]
MFI physical fatigue	0.23[a]	0.27[a]	0.14[a]	0.26[a]	0.11[a]	0.17[a]	0.13[a]	0.07	0.20[a]
MFI reduced activity	0.15[a]	0.25[a]	0.14[a]	0.12[a]	0.05	0.10[a]	0.13[a]	-0.01	0.06

MFI mental fatigue	0.16[a]	0.12[a]	0.14[a]	0.15[a]	0.07	0.19[a]	0.25[a]	0.07[a]	0.05
MFI reduced motivation	0.14[a]	0.14[a]	0.12[a]	0.14[a]	0.13[a]	0.07	0.15[a]	0.02	0.03
HADS anxiety	0.29[a]	0.20[a]	0.14[a]	0.38[a]	0.24[a]	0.24[a]	0.14[a]	0.09[a]	0.19[a]
HADS depression	0.30[a]	0.23[a]	0.20[a]	0.32[a]	0.22[a]	0.21[a]	0.21[a]	0.08	0.15[a]
Brixton R	0.21[a]	0.17[a]	0.15[a]	0.13	0.15[a]	0.04	0.20[a]	0.18[a]	0.06
Brixton S	-0.24[a]	-0.18[a]	-0.14	-0.16[a]	-0.16[a]	-0.05	-0.25[a]	-0.19[a]	-0.10
MMSE	-0.16[a]	-0.11	-0.17[a]	-0.01	-0.03	0.02	-0.30[a]	-0.17[a]	-0.03
Levodopa	0.22[a]	0.19[a]	0.14[a]	0.14[a]	0.09	0.14[a]	0.04	0.22[a]	0.12
Dopamine agonist	0.07	0.00	0.03	0.07	0.02	0.02	0.02	0.09	0.11
Selegeline	0.13	0.17[a]	0.13	0.09	0.03	0.08	0.09	0.03	0.05
Levodopa + Entacapone	-0.31[a]	-0.25[a]	-0.20[a]	-0.26[a]	-0.18[a]	-0.16[a]	-0.16[a]	-0.19[a]	-0.21[a]
Medication other	-0.08	0.09	-0.10	-0.02	-0.14	-0.10	-0.05	-0.15[a]	0.05

[a] $p < 0.05$

Table 2.3 Multilevel regression model to test the effect of confounders on the predictive value of impact of fatigue for health-related quality of life (PDQ-39 summary index), adjusted for treatment allocation (N = 153)

Variables in the model	β Value of candidate confounder (95% CI)	Standardized β value of candidate confounder	β Value of MFI-total (95% CI)	Standardized β value of MFI-total	Proportional change in the coefficient of MFI-total
MFI-total			0.24 (0.18 to 0.30)	0.30[a]	
HADS depression	0.82 (0.53 to 1.11)	0.21[a]	0.17 (0.11 to 0.23)	0.21[a]	30.0%
HADS anxiety	0.88 (0.62 to 1.14)	0.24[a]	0.18 (0.13 to 0.23)	0.23[a]	24.1%
UPDRS III (on)	0.18 (0.10 to 0.26)	0.14[a]	0.22 (0.16 to 0.28)	0.28[a]	7.6%
H&Y (on)	8.23 (5.24 to 11.21)	0.33[a]	0.22 (0.16 to 0.28)	0.28[a]	6.8%
Disease duration	0.91 (0.59 to 1.23)	0.33[a]	0.25 (0.19 to 0.31)	0.32[a]	5.9%
MMSE	-0.67 (-1.65 to 0.31)	-0.09	0.23 (0.17 to 0.29)	0.29[a]	1.7%
Levodopa	0.01 (0.00 to 0.01)	0.20[a]	0.23 (0.17 to 0.29)	0.29[a]	1.7%
Selegeline	2.40 (-2.81 to 7.60)	0.06	0.23 (0.17 to 0.29)	0.29[a]	1.3%
Levodopa + Entacapone	-8.99 (-12.94 to -5.05)	-0.28[a]	0.23 (0.18 to 0.29)	0.29[a]	1.3%
Age	-0.04 (-0.29 to 0.20)	-0.02	0.24 (0.18 to 0.30)	0.30[a]	0.8%
Gender	-2.72 (-6.35 to 0.92)	-0.10	0.24 (0.18 to 0.30)	0.30[a]	0.8%
Medication other	-3.18 (-7.06 to 0.70)	-0.11	0.24 (0.18 to 0.30)	0.30[a]	0.8%
Brixton R	0.24 (0.06 to 0.41)	0.17[a]	0.24 (0.18 to 0.30)	0.30[a]	0.4%
Brixton S	-1.30 (-2.09 to -0.50)	-0.21[a]	0.24 (0.18 to 0.30)	0.30[a]	0.4%
Dopamine agonist	0.74 (-3.11 to 4.59)	0.02	0.24 (0.18 to 0.30)	0.30[a]	0.4%
Social support	-0.37 (-4.87 to 4.13)	-0.01	0.24 (0.18 to 0.30)	0.30[a]	0.0%

[a] $p < 0.05$

Table 2.4 shows that controlling for depression (Hospital Anxiety and Depression Scale) decreased the regression coefficient between PDQ-39 mobility and the Multidimensional Fatigue Inventory physical fatigue subscale by 20.5%. No significant distortion was found for the regression coefficient between PDQ-39 cognitions and the Multidimensional Fatigue Inventory mental fatigue subscale (see Table 2.5).

After multivariate modeling, which included all candidate confounders, the found associations between HRQOL and fatigue remained significant (PDQ-39 summary index-Multidimensional Fatigue Inventory total score, $\beta = 0.12$, 95% confidence interval (CI) = 0.06 to 0.18 ($r^2 = 2.3\%$); PDQ-39 mobility-Multidimensional Fatigue Inventory physical fatigue subscale, $\beta = 0.99$, 95% CI = 0.60 to 1.38 ($r^2 = 3.4\%$); PDQ-39 cognitions-Multidimensional Fatigue Inventory mental fatigue subscale, $\beta = 1.01$, 95% CI = 0.70 to 1.31 ($r^2 = 5.0\%$)).

Discussion

This prospective cohort study is the first to show a significant longitudinal association between impact of fatigue and poorer overall HRQOL in patients with Parkinson's disease. However, this longitudinal association is significantly distorted by depression and anxiety. After controlling for these confounders, fatigue was still significantly associated with overall HRQOL. These findings confirm our hypothesis that the impact of fatigue is an independent factor that contributes to a reduced perception of HRQOL when measured repeatedly over three months' time in patients with moderate to severe Parkinson's disease.

The relationship found between impact of fatigue and HRQOL suggests that patients who experience more fatigue also report lower levels of overall HRQOL. However, the explained variance of HRQOL by impact of fatigue was small ($r^2 = 2.3\%$), suggesting that the unique contribution of fatigue is only a minor almost negligible factor in the complex array of symptoms that determines overall HRQOL in patients with Parkinson's disease.

Our results are in line with a cross-sectional study [4] that investigated the relationship between fatigue (Fatigue Severity Scale) and disease-specific HRQOL (PDQ-39). These authors found a small but statistically significant association between the impact of fatigue and overall HRQOL. In contrast, two other cross-sectional studies [5, 6] found no statistically significant association between impact of fatigue and overall HRQOL. Both studies used the PDQ-39 to assess HRQOL; however, different instruments were used to measure the impact of fatigue. McKinlay and colleagues [5] used an adapted

Table 2.4 Multilevel regression model to test the effect of confounders on the predictive value of physical fatigue for physical aspects of health-related quality of life (PDQ-39 mobility), adjusted for treatment allocation (N = 153)

Variables in the model	β Value of candidate confounder (95% CI)	Standardized β value of candidate confounder	β Value of MFI physical fatigue (95% CI)	Standardized β value of MFI physical fatigue	Proportional change in the coefficient of MFI physical fatigue
MFI physical fatigue			1.46 (1.09 to 1.84)	0.27[a]	
HADS depression	1.10 (0.60 to 1.60)	0.16[a]	1.16 (0.77 to 1.56)	0.22[a]	20.5%
HADS anxiety	1.00 (0.57 to 1.43)	0.16[a]	1.26 (0.89 to 1.64)	0.23[a]	13.7%
H&Y (on)	17.08 (12.26 to 21.89)	0.40[a]	1.35 (0.98 to 1.72)	0.25[a]	7.5%
UPDRS III (on)	0.46 (0.31 to 0.62)	0.22[a]	1.38 (1.00 to 1.75)	0.25[a]	5.9%
Disease duration	1.12 (0.54 to 1.69)	0.24[a]	1.54 (1.16 to 1.91)	0.28[a]	5.1%
Selegeline	7.93 (-0.76 to 16.62)	0.12	1.43 (1.05 to 1.81)	0.26[a]	2.4%
Age	0.30 (-0.10 to 0.71)	0.09	1.43 (1.05 to 1.81)	0.27[a]	2.1%
Brixton S	-1.81 (-3.17 to -0.44)	-0.17[a]	1.49 (1.11 to 1.88)	0.28[a]	2.1%
Levodopa	0.01 (0.00 to 0.02)	0.16[a]	1.43 (1.06 to 1.81)	0.27[a]	2.0%
Brixton R	0.34 (0.04 to 0.64)	0.14[a]	1.48 (1.10 to 1.87)	0.27[a]	1.4%
MMSE	-0.94 (-2.62 to 0.74)	-0.07	1.45 (1.07 to 1.82)	0.27[a]	1.1%
Social support	-5.75 (-13.39 to 1.89)	-0.10	1.45 (1.07 to 1.82)	0.27[a]	1.0%
Dopamine agonist	-1.89 (-8.50 to 4.72)	-0.04	1.48 (1.10 to 1.86)	0.27[a]	1.0%
Levodopa + Entacapone	-12.97 (-19.84 to -6.09)	-0.23[a]	1.46 (1.08 to 1.83)	0.27[a]	0.5%
Gender	-8.24 (-14.34 to -2.14)	-0.17[a]	1.47 (1.09 to 1.84)	0.27[a]	0.4%
Medication other	2.86 (-3.80 to 9.53)	0.06	1.46 (1.08 to 1.84)	0.27[a]	0.2%

[a] $p < 0.05$

Table 2.5 Multilevel regression model to test the effect of confounders on the predictive value of mental fatigue for cognitive aspects of health-related quality of life (PDQ-39 cognitions), adjusted for treatment allocation (N = 153)

Variables in the model	β Value of candidate confounder (95% CI)	Standardized β value of candidate confounder	β Value of MFI mental fatigue (95% CI)	Standardized β value of MFI mental fatigue	Proportional change in the coefficient of mental fatigue
MFI mental fatigue			1.14 (0.84 to 1.43)	0.25[a]	
HADS depression	0.86 (0.36 to 1.37)	0.16[a]	1.02 (0.72 to 1.32)	0.23[a]	10.0%
HADS anxiety	0.49 (0.13 to 0.84)	0.10[a]	1.05 (0.75 to 1.36)	0.23[a]	7.2%
MMSE	-2.36 (-3.63 to -1.10)	-0.23[a]	1.07 (0.77 to 1.37)	0.24[a]	5.5%
Brixton R	0.32 (0.09 to 0.54)	0.17[a]	1.20 (0.89 to 1.50)	0.27[a]	5.2%
Brixton S	-1.72 (-2.77 to -0.68)	-0.20[a]	1.18 (0.88 to 1.48)	0.26[a]	4.1%
Disease duration	0.70 (0.25 to 1.15)	0.19[a]	1.17 (0.87 to 1.46)	0.26[a]	2.8%
Selegeline	3.02 (-3.64 to 9.68)	0.06	1.12 (0.82 to 1.42)	0.25[a]	1.5%
Levodopa + Entacapone	-5.72 (-11.14 to -0.30)	-0.13[a]	1.12 (0.82 to 1.42)	0.25[a]	1.3%
Medication other	-1.05 (-6.16 to 4.06)	-0.03	1.12 (0.82 to 1.42)	0.25[a]	1.2%
Dopamine agonist	0.02 (-5.04 to 5.08)	0.00	1.12 (0.83 to 1.42)	0.25[a]	1.1%
Levodopa	0.00 (-0.01 to 0.01)	0.02	1.12 (0.83 to 1.42)	0.25[a]	1.1%
Gender	4.88 (0.12 to 9.63)	0.13[a]	1.13 (0.83 to 1.42)	0.25[a]	1.0%
UPDRS III (on)	0.02 (-0.11 to 0.15)	0.01	1.13 (0.82 to 1.43)	0.25[a]	0.9%
H&Y (on)	5.89 (1.81 to 9.96)	0.17[a]	1.13 (0.83 to 1.43)	0.25[a]	0.7%
Age	0.24 (-0.07 to 0.55)	0.10	1.13 (0.83 to 1.43)	0.25[a]	0.4%
Social support	1.45 (-4.46 to 7.35)	0.03	1.13 (0.84 to 1.43)	0.25[a]	0.2%

[a] $p < 0.05$

version of the Fatigue Severity Scale in which patients were asked to answer each original item separately for both mental and physical fatigue, whereas Havlikova [6] used the Multidimensional Fatigue Inventory general fatigue subscale to measure impact of fatigue. The use of different questionnaires may explain the inconsistent findings between these studies, as different questionnaires measure different aspects or constructs of fatigue [8].

As expected, physical fatigue (Multidimensional Fatigue Inventory physical fatigue subscale) was most strongly associated with the PDQ-39 mobility domain. Interestingly, Havlikova and colleagues [6] found no association between the Multidimensional Fatigue Inventory physical fatigue subscale and PDQ-39 mobility but found that other aspects of physical fatigue (assessed with the Multidimensional Fatigue Inventory reduced activity subscale) were significantly associated with PDQ-39 mobility. In addition, in another longitudinal study that used ambulatory accelerometry to measure physical activity [7], we found a significant association between the Multidimensional Fatigue Inventory physical fatigue subscale and percentage time performing physical activity. Our current finding that mental fatigue was most strongly associated with cognitive aspects of HRQOL is in agreement with previous findings [6].

Since neuropsychiatric problems, such as depression and anxiety, have been related with poorer overall HRQOL in patients with Parkinson's disease and show considerable symptom overlap with fatigue [5], it is likely that the distortion of the regression coefficients between fatigue and HRQOL by depression and anxiety is caused by confounding. This suggests that the evaluation of fatigue should at least be accompanied by the assessment of depression and anxiety. However, both depression and fatigue have also been observed as independent symptoms in patients with Parkinson's disease [1], therefore clinicians have to be careful labelling patients with fatigue as being depressed.

In the present study, medication intake did not significantly distort the association between impact of fatigue and HRQOL. However, as medication intake was measured categorically, it is difficult to draw valid conclusions about the effect of dose of medication on the relationship between fatigue and HRQOL.

The strength of this study is the use of repeated measurements in time to investigate the association between impact of fatigue and HRQOL. Although the used random coefficient analysis model provides a pooled regression coefficient that reflects both the cross-sectional (between subjects) and longitudinal (within subject) relationship, no separation can be made between these two aspects. If the variation in absolute values between subjects exceeds the changes over time within subjects, the interpretation

of the longitudinal construct validity between impact of fatigue and HRQOL may be limited [22]. Future research, that emphasizes the within-subject variation, may provide additional data on the interpretation of the longitudinal construct validity between impact of fatigue and HRQOL in patients with Parkinson's disease.

There are some study limitations that should be acknowledged. First, both HRQOL and impact of fatigue are subjective measures that are difficult to assess. Although the PDQ-39 is commonly used to measure disease-specific HRQOL in patients with Parkinson's disease, the grouping of items into domains appears complex and the meaning of the domain scores is unclear, which may hamper interpretation [23]. In addition, a recent study that investigated the structural validity of the Multidimensional Fatigue Inventory [17] did not reproduce the originally proposed Multidimensional Fatigue Inventory physical fatigue subscale in patients with Parkinson's disease and suggested that combining the Multidimensional Fatigue Inventory general fatigue and physical fatigue dimensions into one subscale may more validly measure the different aspects of fatigue compared to the originally proposed five dimensions. Second, we did not control for sleep disorders and apathy. It is conceivable that sleep disorders could have distorted the association between fatigue and HRQOL. Previous research, however, concluded that fatigue was not cross-sectionally related to daytime sleepiness and nighttime sleep dysfunction [24]. Apathy might have affected HRQOL and could have distorted the association between fatigue and HRQOL. Finally, the present study was part of a randomized clinical trial in which patients received cueing therapy. Patients were excluded if they had cognitive impairments or comorbid conditions that interfered with participation in cueing training. This may limit the external validity of the longitudinal regression models. Furthermore, cueing therapy may have influenced the longitudinal association between impact of fatigue and HRQOL. However, we did correct the multivariate models for treatment allocation, arguably minimizing the impact of the intervention. In addition, cueing therapy had no significant effect on perceived HRQOL [10].

In conclusion, impact of fatigue is longitudinally associated with poorer overall HRQOL; however, this association is heavily confounded by depression and anxiety and the unique contribution of fatigue to overall HRQOL is small. When evaluating fatigue in patients with Parkinson's disease, the influence of depression and anxiety should therefore be considered. A comprehensive test battery that encompasses different neuropsychiatric symptoms may be helpful in this regard. Future studies should focus on the longitudinal association between fatigue and other neuropsychiatric symptoms to determine underlying causal pathways that contribute to HRQOL.

Clinical messages

- Evaluation of fatigue in patients with Parkinson's disease should be accompanied by the assessment of depression and anxiety.
- Patients who experience fatigue report lower levels of overall HRQOL. However, fatigue is only a minor factor that determines overall HRQOL in patients with Parkinson's disease.

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