Research Article

Parkinson's Disease Motor and Non-Motor Features Accompanying Insomnia and Excessive Daytime Sleepiness Symptoms, a Large Population-Based Study

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Abstract

Insomnia and excessive daytime sleepiness are the most common sleep disturbances in Parkinson's disease. This study aims at better understanding how severity of PD motor and non-motor features and dopaminergic treatments contribute to these sleep symptoms in the first decade of PD. Data from a community-based cohort of PD patients was used to model cross-sectional PD-related risk factors for insomnia and EDS sleep scores using linear regression models adjusted for age, gender, and PD duration. Longitudinal changes in sleep scores were assessed with paired t-tests. For 481 patients who completed the MOS-Sleep

questionnaire at least once, high levodopa daily doses (500mg+) and severe autonomic and complex non-motor symptoms (depression, anxiety, apathy, hallucinations and dopamine dysregulation syndrome) were associated with both EDS and insomnia symptoms. Higher total motor UPDRS and especially tremor sub-scores and motor complications were associated only with insomnia, while axial/posture/gait and body bradykinesia UPDRS sub-scores were associated only with EDS. In 156 patients, with a second sleep measure on average after 2.2 years of follow-up, only EDS scores increased over time. Groups defined by worse PD features severity at first follow-up (UPDRS 35+, PD duration 6.5+ years, or LED 500mg+) had larger average increases in EDS score over time. These findings provide evidence that motor and non-motor dysfunction in PD are associated with insomnia and EDS symptoms, but specific features and level of severity affect sleep symptoms differently. Motor manifestations related to tremor and dyskinesia are associated with sleep quantity and quality, measured by insomnia symptoms, while axial motor features are related to EDS symptoms.

Keywords

Parkinson's disease; motor symptoms; non-motor symptoms; sleep problems; circadian dysfunction; insomnia; excessive daytime sleepiness

1. Introduction

Sleep disturbances have been increasingly recognized as important non-motor components of the Parkinson's disease (PD) syndrome [1-5]. The most frequent sleep or sleep-related problems that patients report are excessive daytime sleepiness (EDS), insomnia and REM sleep behavior disorder (RBD) [6]. Insomnia and EDS are sleep-wake disturbances that may indicate disruption of the circadian rhythm as part of the neurodegenerative process characteristic of PD [7, 8].

Insomnia is the difficulty to initiate or maintain sleep and, when it manifests chronically, insomnia has well-known negative consequences for health and quality of life [9, 10]. While PD patients usually do not have trouble initiating sleep, insomnia manifests mainly as the difficulty to maintain sleep, resulting in sleep fragmentation and early awakening [11]. EDS refers to a subjective complaint characterized by difficulty in remaining awake during the day, usually accompanied by sleep initiation if the person stays inactive [12], and it is more common in PD patients than in the general population [13]. EDS can be secondary to other sleep disorders and health factors, or can be attributable to primary central disorders of hypersomnolence, as defined in the International Classification of Sleep Disorders (ICSD) [14].

Better insight into what causes sleep problems in PD will encourage improvements in clinical care and quality of life of patients. In the last decade, a number of studies suggested the following risk factors for insomnia and/or EDS in PD [15-24]: PD duration, motor disability, dopaminergic medications, depression and anxiety, and autonomic symptoms. However, these studies mainly enrolled patients from tertiary clinics or, when community-based, they were conducted in European countries or had a small number of participants. Also, they yielded conflicting results as to which PD-related clinical symptoms are related to sleep disorders. Previously, data from a large community-based cohort of PD patients was analyzed to investigate the role of REM sleep behavior

disorder on PD progression [25]. Relying on the same cohort of PD patients, the present study assesses contributions of severity of PD motor and non-motor features and treatment with levodopa to insomnia and EDS symptoms in patients who are, on average, within six years (range: 2 - 15) of an initial PD diagnosis.

2. Methods

2.1 Study Design

The Parkinson's Environment and Genes Study (PEG), identified new-onset (up to 5 years after diagnosis) PD cases at baseline from 2001 to 2007 (PEG 1), and from 2011 to 2017 (PEG 2), from the entire population of three California counties [26]. PEG 1&2 participants were seen for a first follow-up, on average 3.2 years after their baseline visit. PEG 1 participants were additionally seen a second time, on average 2.2 (±0.5) years later. At all time points, participants were examined at a local clinic by PEG study movement disorders specialists, who confirmed the diagnosis according to common criteria [26], and evaluated motor signs and symptoms, preferably with patients "off" PD medications.

The UCLA Institutional Review Board approved all phases of the study protocol, and participants were informed of all procedures and their rights and provided written informed consent.

2.2 Data Collected

Study neurologists examined patients and scored motor disability using the Unified Parkinson's Disease Rating Scale (UPDRS, and later MDS-UPDRS), parts III and IV and Hoehn and Yahr staging (HY). The exams were preferably conducted with patients "off" PD medications (>90% of exams were "off"). UPDRS-III scores were corrected for missing items that cannot be evaluated (such as arising from chair in paraplegic patients), and when only an "on medication" exam was possible, as previously described [27]. PD motor subtypes of Postural Imbalance and Gait Dysfunction (PIGD), Tremor Dominant (TD), or indeterminate were calculated as ratios of UPDRS-III sub-scores, as described previously [28]. PD medication information, including levodopa and dopamine agonist use, were summarized into a daily levodopa equivalent dose (LED) [29].

During all visits, trained research assistants interviewed participants to collect demographic, lifestyle, and medical history information, including current PD medication use and dosage. We calculated UPDRS-III motor total score and sub-scores; the latter by summing specific items corresponding to total tremor [30] (rest and postural), rigidity, limb bradykinesia [31] (fingers tapping, hands grip, hands rapid movements, leg agility), and axial/posture/gait [31] (speech, facial expression, arise from chair, posture, postural stability, gait, and body bradykinesia).

Additional standardized instruments were adopted only during follow-up, including those measuring insomnia and EDS, as well as the UPDRS-IA, IB and II to assess non-motor and motor impacts of PD on experiences of daily living. We rely on the Sleep Survey of the Medical Outcomes Study (MOS-Sleep) for recording symptoms of insomnia and EDS. It contains twelve items, each with six answer options on a Likert scale, measuring subjective experiences of sleep in the past four weeks across several domains including sleep initiation, maintenance, quantity/duration, perceived adequacy, respiratory problems and somnolence. The MOS-Sleep has been validated and been used to study chronic diseases; its content is very comparable to two questionnaires widely used in PD

sleep research, the Pittsburgh Sleep Quality Index (PSQI) and the Parkinson's Disease Sleep Scale (PDSS) [32].

MOS-Sleep items are summarized to create five scores (sleep disturbance, somnolence, sleep adequacy, snoring, and shortness of breath during sleep) ranging from 0 to 100, with higher scores indicating worse sleep quality, except for the adequacy score, which is reversed. For this study's purposes, we adopted the continuous scores (0 to 100) for sleep disturbance (items: having trouble falling asleep, how long to fall asleep, sleep was not quiet, awake during sleep time, and having trouble falling asleep again) as a measure of insomnia symptoms, and for somnolence (items: drowsy during day, having trouble staying awake during the day, taking naps), as a measure of EDS symptoms.

2.3 Statistical Analysis

Analyses were conducted in statistical software SAS (SAS 9.4, SAS Institute, Cary, NC), figures were generated in R. Insomnia and EDS scores were normally distributed univariately and across risk factors of interest; such as gender, age and PD duration at the time sleep measures.

Sleep scores were z-standardized, centering on mean 0 and standard deviation 1. First, mean crude z-standardized MOS-Sleep scores by patients' characteristics were estimated. To visualize how PD-related factors (PD duration, age at diagnosis, UPDRS-III, UPDRS-IA, and LED) may influence sleep symptoms, crude z-standardized insomnia and EDS scores were plotted according to these PD-related factors, stratifying by gender, and generating Pearson correlation coefficients.

Adjusted mean differences in sleep scores between binary measures of PD severity were modeled using linear regressions (implemented with maximum likelihood in Proc Genmod; SAS 9.4) including potential confounders as covariates; i.e., at a minimum we included gender, age at interview, and PD duration. PD measures were dichotomized, i.e., at the median for PD duration (6.5 years) at first sleep assessment; at 35 points for the UPDRS-III motor; at 500 mg for the LED as proposed previously [17]; for the UPDRS-II (20 points), UPDRS-IA (5 points), and the autonomic symptoms score (8 points) the cut-points correspond to the respective 75th percentile of the score. To estimate associations between UPDRS motor sub-scores with insomnia and EDS scores, similar adjusted linear regression models were used, but continuous motor sub-scores were also z-standardized and results presented as β-coefficients. In sensitivity analyses, additional potential confounders were included guided by mechanisms proposed and depicted in Directed Acyclic Graphs [33] (Supplemental Figure S1) as detailed in Results.

In a subset of the PEG1 cohort with information on sleep measures (n=156) at an additional follow-up time, average sleep scores at both follow-up times stratified by PD severity measures were compared using t-tests as well as paired t-tests to identify differences in average sleep scores over time by PD-severity at first follow-up (between and within groups).

3. Results

This study included 481 PD patients who completed the MOS-Sleep at least once, of whom 459 (95%) also completed a simultaneous motor examination. The majority was male (62%), White (77%), assessed for sleep quality on average 6.3 ± 3.0 years after their first PD diagnosis, and 69% exhibited a PIGD motor phenotype (Table 1). Among the sleep domains the MOS assesses, EDS received the highest absolute score, on a scale from 0 to 100 (mean 42.4 ± SD 23.7), followed by

snoring (34.5 ± 33.4) and insomnia (30.5 ± 22.6). Insomnia and EDS measures were moderately positively correlated (ρ=0.34) (Supplemental Figure S2). Figure 1 shows linear correlations of MOS-Sleep scores with PD-related measures; patients diagnosed at younger ages and with longer PD duration had worse insomnia symptom scores, but these PD features were not correlated with EDS (Figure 1). All other PD-related measures were positively correlated with both insomnia and EDS, in men and women.

Table 2 presents cross-sectional mean differences in insomnia and EDS scores comparing groups defined by PD severity, adjusting for gender, age and PD duration. In these models, a PD duration of 6.5+ years was associated with higher EDS, but not insomnia. Conversely, a UPDRS-III motor total score of 35+ and the presence of motor complications were associated with higher average insomnia scores, but not with EDS. Specifically, off-dystonia and motor fluctuations were the motor complications associated with worse insomnia scores. Estimates for motor complications remained unchanged in models further adjusted for levodopa use or dose, and for UPDRS-III scores. Likewise, the strong positive associations of non-motor (UPDRS-IA) and autonomic symptoms with insomnia and EDS scores persisted when the models were further adjusted for UPDRS-III or levodopa dose.

Only few patients did not take PD medications (8%) or solely used dopamine agonists (6%), while 54% were treated with levodopa only, and 32% with a combination of levodopa and dopamine agonists (Table 1). Patients with LED ≥500mg had worse insomnia and EDS symptoms, compared to the group with <500mg, while higher doses of dopamine agonists (≥200mg vs. <200mg) did not significantly impact the sleep scores. These estimates remained unchanged in models that included the motor UPDRS-III scores, or axial/postural/gait or tremor sub-scores (results not shown).

Table 1 Distribution of demographics, PD-related characteristics and MOS-Sleep scale scores for Insomnia and EDS, at first follow-up.

| | | N (%) | Crude Mean Standardized MOS-Sleep score | |
			Insomnia (Mean ± SD)	EDS (Mean ± SD)
Total		481 (100)	0 ± 1	0 ± 1
Study cohort[1]	PEG 1	234 (49)	-0.051 ± 0.978	0.034 ± 0.978
	PEG 2	247 (51)	0.049 ± 1.020	-0.033 ± 1.022
Age at interview	65 or less	119 (25)	0.299 ± 1.139	0.040 ± 1.026
	66 to 80	263 (55)	-0.107 ± 0.895	-0.013 ± 0.937
	more than 80	95 (20)	-0.078 ± 1.026	-0.013 ± 1.136
Gender	women	183 (38)	0.002 ± 0.993	-0.226 ± 0.942
	men	298 (62)	-0.001 ± 1.006	0.141 ± 1.010
Ethnicity	White	371 (77)	-0.057 ± 0.959	0 ± 0.985
	Latino	79 (17)	0.183 ± 1.112	-0.059 ± 1.060
	Other	29 (6)	0.228 ± 1.124	0.160 ± 1.043
Education	<12 years	71 (15)	0.259 ± 1.097	-0.037 ± 1.064
	12+	411 (85)	-0.045 ± 0.978	0.009 ± 0.989
Age at PD diagnosis	≤60	131 (27)	0.284 ± 1.136	0.089 ± 1.034
	>60	350 (73)	-0.104 ± 0.925	-0.033 ± 0.987

Age at PD duration	≤6.5 years	279 (58)	-0.120 ± 0.906	-0.131 ± 0.948
	>6.5 years	202 (42)	0.168 ± 1.099	0.183 ± 1.043
Motor subtype (missing=27)	tremor dominant or indeterminate	151 (33)	-0.032 ± 0.939	-0.074 ± 0.969
	PIGD	303 (67)	0.030 ± 1.025	0.035 ± 0.990
UPDRS-III[2] total score	<35 (missing= 22)	349 (76)	-0.054 ± 0.957	-0.041 ± 0.951
	35+	110 (24)	0.235 ± 1.107	0.146 ± 1.082
Hoehn and Yahr	stages 0-2.5 (missing= 33)	330 (74)	-0.011 ± 0.973	-0.063 ± 0.957
	stage 3+	118 (26)	-0.025 ± 1.054	0.105 ± 0.991
LED[3] Dopamine agonists only, 200 mg+		114 (25)	0.036 ± 1.001	0.009 ± 0.929
LED[3] Levodopa only, 500 mg+		188 (40)	0.164 ± 1.064	0.240 ± 1.046
LED[3] total, 600 mg+		197 (42)	0.154 ± 1.063	0.146 ± 1.039
UPDRS-IV[4] (motor complications) any present (missing= 22)		235 (53)	0.200 ± 1.051	0.041 ± 0.923
UPDRS-IV sub-scores	Dyskinesia, present[5]	97 (22)	0.259 ± 1.027	0.031 ± 0.896
	Motor Fluctuations, present	190 (43)	0.223 ± 1.036	0.015 ± 0.941
	Off-Dystonia, present	77 (17)	0.380 ± 1.119	0.183 ± 0.956
UPDRS-II[6] (motor ADL) score, 20+		140 (32)	0.269 ± 1.092	0.305 ± 1.011
UPDRS-IA (non-motor, complex behaviours)[7]	score 5+	114 (25)	0.450 ± 1.121	0.359 ± 0.974
	Autonomic sympoms[8], score 8+	118 (25)	0.177 ± 1.051	0.331 ± 0.959
	Urinary problems, present	350 (74)	0.070 ± 1.013	0.100 ± 0.999

1. PEG=Parkinson's Environment and Genes.

2. UPDRS-III (rated by physician), motor signs: speech, facial expression, tremor at rest (face, hands, feet) amplitude and constancy, rigidity (neck, arms, legs), fingers and toes tapping, hand grip and movements, leg agility, arising from chair, posture, gait and freezing of gait, postural stability, body bradykinesia, postural and kinetic tremor.

3. LED: Levodopa Equivalent Daily Dose.

4. UPDRS-IV (applied by physician), motor complications items: dyskinesias (time spent and functional impact), motor fluctuations (time spent in off-state, functional impact and complexity of fluctuations), painful off-state present and time spent.

5. Presence of dyskinesia: measured by UPDRS-IV question "Time Spent with Dyskinesias", where option "0=Normal" corresponds to "No Dyskinesia" and any other option (1,2,3 or 4) corresponds to "Yes Dyskinesia".

6. UPDRS-II: Motor Aspects of Experiences of Daily Living (self-completed) items: speech, saliva/drooling, chewing/swallowing, eating, dressing, hygiene, handwriting, hobbies, turning in bed, tremor, getting off bed/car/chair, walking/balance, freezing.

7. UPDRS-I: Non-Motor Aspects of Experiences of Daily Living.

8. UPDRS-IA (rated by physician), complex behaviours items: cognitive impairment, hallucinations, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome.

9. Autonomic symptoms score: constipation, urinary, light headedness, saliva/drooling, chewing/swallowing.
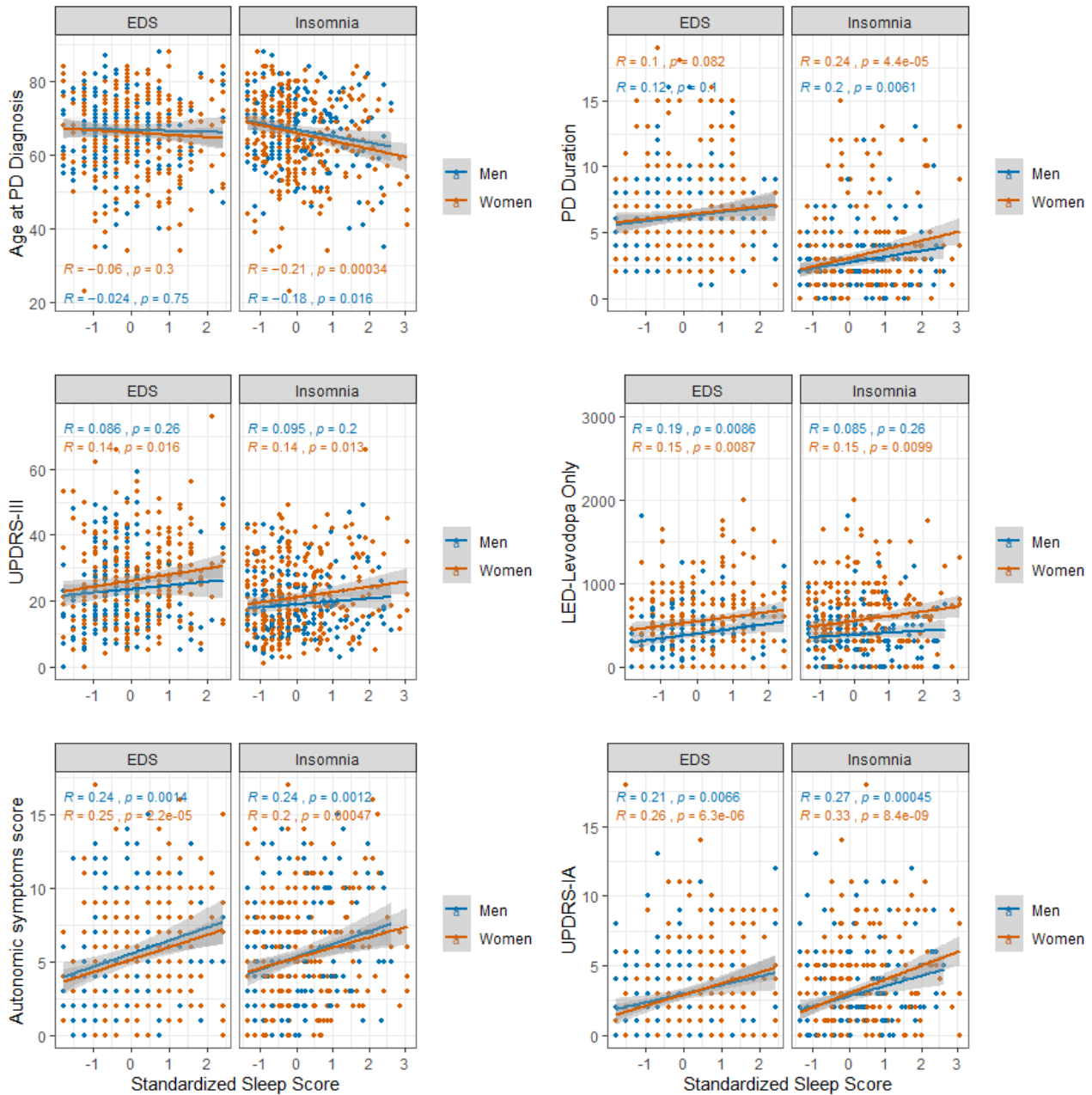
Figure 1 Scatterplot of standardized sleep scores (mean 0, SD 1) by PD characteristics stratified by gender. Including best fit linear correlation line, Pearson correlation coefficients, and p-values. N=481 (except for UPDRS-III, N=459).

Table 2 Linear regressions of insomnia and EDS scores on PD-related characteristics (**cross-sectional**), adjusted for gender, age and duration of Parkinson's disease in years, N=459.

PD severity measures (binary)	Insomnia	EDS
	Mean difference[1] (95% CI)	
PD duration[2], years, 6.5+ vs. < 6.5	0.02 (-0.26, 0.29)	0.34 (0.06, 0.62)
UPDRS-III[3] total score, 35+ vs. < 35	0.27 (0.06, 0.49)	0.14 (-0.07, 0.35)
HY, stage 3+ vs. stage< 3 (Total N= 448)	0.08 (-0.13, 0.29)	0.19 (-0.02, 0.40)
Motor subtype, PIGD[4] vs. other	0.12 (-0.07, 0.32)	0.14 (-0.05, 0.33)
LED[5], Levodopa only, 500mg+ vs. <500mg	0.22 (0.03, 0.41)	0.29 (0.10, 0.47)
Only dopamine agonists, 200mg+ vs. <200mg	-0.10 (-0.32, 0.11)	-0.05 (-0.26, 0.17)
Total, Levodopa and dopamine agonists, 600mg+ vs. <600mg	0.17 (-0.02, 0.35)	0.15 (-0.04, 0.34)
UPDRS-IV[6] total (motor complications), any present vs. not	0.25 (0.06, 0.44)	0.04 (-0.15, 0.23)
UPDRS-IV, Dyskinesia[7], present vs. not	0.13 (-0.10, 0.36)	-0.04 (-0.27, 0.19)
Motor Fluctuations, present vs. not	0.24 (0.05, 0.43)	-0.02 (-0.20, 0.17)
Off-Dystonia, present vs. not	0.33 (0.09, 0.58)	0.23 (-0.01, 0.47)
UPDRS-II[8] score, 20+ vs. <20	0.37 (0.18, 0.57)	0.40 (0.20, 0.60)
UPDRS-IA[9] score, 8+ vs. <8	0.54 (0.34, 0.74)	0.45 (0.25, 0.65)
Autonomic symptoms[10] score, 5+ vs. < 5	0.27 (0.06, 0.48)	0.43 (0.23, 0.64)
Urinary problems, present vs. not	0.27 (0.07, 0.47)	0.32 (0.12, 0.52)

1. Adjusted for gender, age, and duration of PD.

2. Adjusted for gender and age.

3. UPDRS-III (rated by physician), motor signs: speech, facial expression, tremor at rest (face, hands, feet) amplitude and constancy, rigidity (neck, arms, legs), fingers and toes tapping, hand grip and movements, leg agility, arising from chair, posture, gait and freezing of gait, postural stability, body bradykinesia, postural and kinetic tremor.

4. Postural Instability and Gait Disturbance (or Dysfunction, Difficulty)

5. LED: Levodopa Equivalent Daily Dose

6. UPDRS-IV (applied by physician), motor complications items: dyskinesias (time spent and functional impact), motor fluctuations (time spent in off-state, functional impact and complexity of fluctuations), painful off-state present and time spent.

7. Presence of dyskinesia: measured by UPDRS part IV question "Time spent with dyskinesias", where option "0=Normal" corresponds to "no dyskinesia" and any other option (1,2,3 or 4) corresponds to "yes Dyskinesia"

8. UPDRS-II (self-completed), motor aspects of experiences of daily living items: speech, saliva/drooling, chewing/swallowing, eating, dressing, hygiene, handwriting, hobbies, turning in bed, tremor, getting off bed/car/chair, walking/balance, freezing.

9. UPDRS-IA (rated by physician), complex behaviors items: cognitive impairment, hallucinations, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome.

10. Autonomic symptoms score: constipation, urinary, light headedness, saliva/drooling, chewing/swallowing**.**

Table 3 shows adjusted linear associations of UPDRS-III motor sub-scores with insomnia and EDS. Total tremor and limb bradykinesia were positively associated only with worse insomnia, while axial/postural/gait was associated only with EDS scores, however, these associations were greatly attenuated in models adjusted for (levodopa-only) LED (results not shown). The association of the body bradykinesia sub-score with EDS persisted after adjustment for LED, but was greatly reduced after adjustment for the geriatric depression scale (GDS) score (β= 0.06; 95% CI: -0.03, 0.15).

Table 3 Linear regressions of insomnia and EDS scores on UPRDS-III motor sub-scores (**cross-sectional**), adjusted for gender, age and duration of Parkinson's disease in years. Sleep scores and motor sub-scores are z-standardized, N=459.

UPDRS-III motor sub-scores, per 1 SD increase	Insomnia β Coefficient (95% CI)	EDS β Coefficient (95% CI)
Total tremor	0.09 (0.00, 0.18)	0.04 (-0.05, 0.13)
Limb bradykinesia	0.11 (0.02, 0.21)	0.06 (-0.03, 0.15)
Rigidity	0.05 (-0.04, 0.15)	-0.01 (-0.11, 0.08)
Axial, posture and gait	0.07 (-0.03, 0.17)	0.10 (0.00, 0.20)
Body bradykinesia	-0.01 (-0.10, 0.09)	0.10 (0.01, 0.19)

Longitudinal information on insomnia and EDS scores was available for 156 participants from the PEG1 study cohort at a second follow-up, on average 2.2 ± 0.5 years after the first, and an average PD duration of 7.4 ± 2.5 years (for the PEG2 cohort a second follow-up has not yet been completed). Of the patients not seen for a second follow-up in PEG1, the majority (65%) had died or were too ill, including cognitive dysfunction. Changes in average MOS-Sleep scores over time were minor. Overall, EDS scores slightly increased from first to second follow-up, the within-person average difference was 3.0 (95% CI: -0.7, 6.6) points on the non-standardized score, i.e., on a scale from 0 to 100, whereas insomnia average scores did not change (-1.4, 95% CI: -4.6, 1.8). Figure 2 shows average within-person changes in insomnia and EDS scores, by PD severity measures, with t-tests comparing scores between groups at each follow-up time. At first follow-up, the severity measures UPDRS ≥ vs. <35 and LED ≥ vs.<500mg and a longer PD duration (≥ vs. <6.5y) were associated with worse concurrent insomnia scores, but these measures did not predict worsening of insomnia scores at the second follow-up. For EDS, on the other hand, higher PD severity and longer duration at first follow-up were associated with worse EDS scores at the second follow-up.
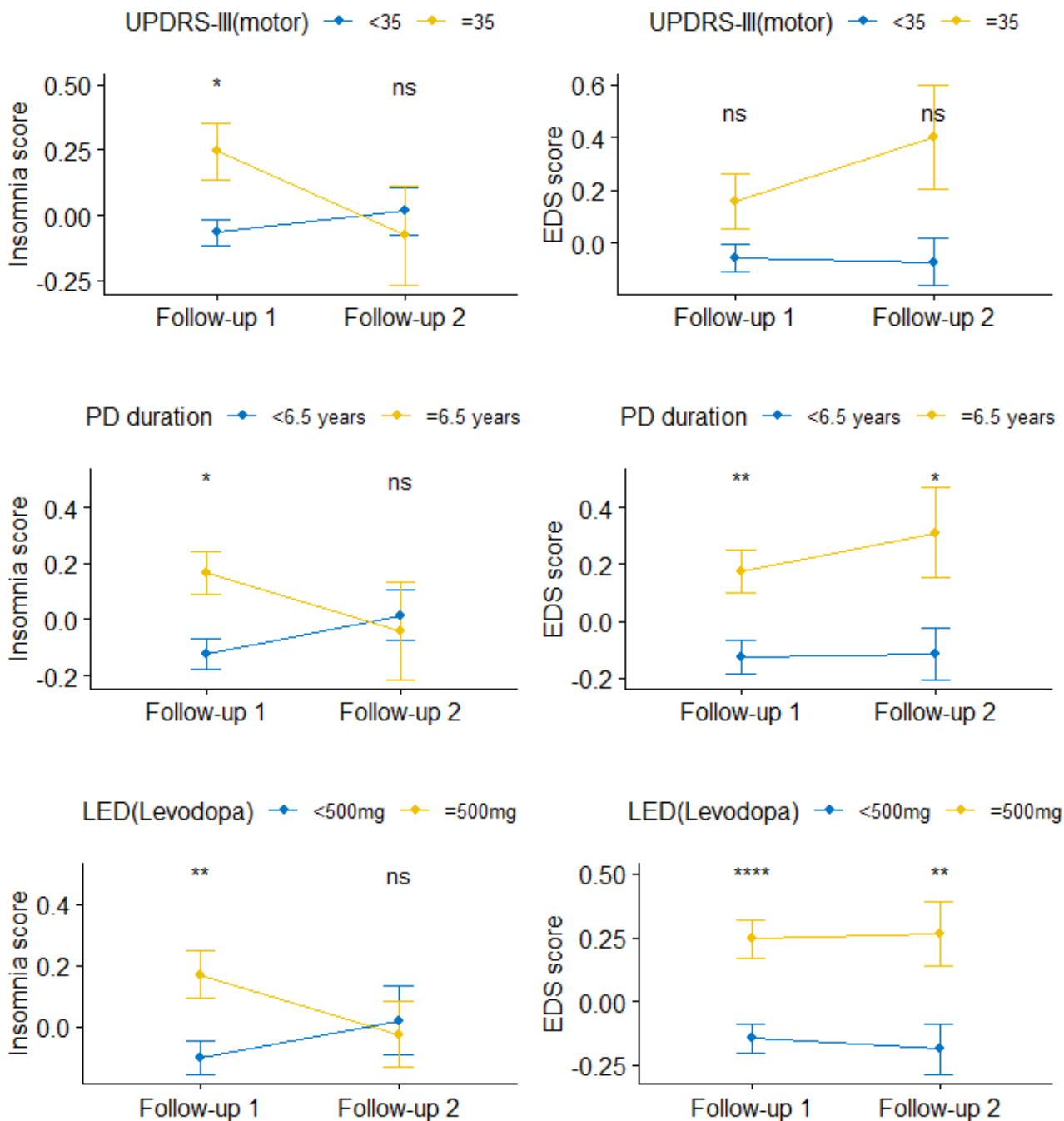
Figure 2 Change in sleep scores from follow-up 1 to follow-up 2 (N=156), by PD severity measures at follow-up 1. Results of significance for t-test: *= p<0.05, **= p<0.01, ****=p<0.0001, ns= p>0.05.

4. Discussion

This large population-based study of Parkinson's disease assessed associations of PD clinical characteristics with insomnia and EDS symptoms among patients with on average six years of disease duration. For a subgroup of 156 patients, sleep information was collected again two years later. In this cohort, virtually all aspects of PD severity evaluated were associated either with worse insomnia, EDS, or with both sleep symptoms, confirming the burden of this non-motor problem during the progression of PD. Total motor UPDRS-III scores, sub-scores of tremor and limb bradykinesia, and UPDRS-IV motor fluctuations were associated with worse insomnia symptoms but not with EDS. Other aspects of PD, such as longer disease duration and motor sub-scores of axial/posture/gait and body bradykinesia were associated only with EDS symptoms. Levodopa doses ≥500mg and autonomic symptoms were associated with worse scores for both sleep problems. For the group with one additional follow-up, only EDS scores were slightly worse after 2.2 years on average, while insomnia scores remained similar.

Neurodegeneration of sleep-wake regulatory centers in PD resulting in circadian disruption [34] is one possible explanation for the association between worse total motor scores and insomnia. The finding that motor UPDRS total score and sub-scores of tremor, limb bradykinesia and motor fluctuations affect only insomnia symptoms can also indicate that these motor manifestations directly disrupt nighttime sleep. Since this study's patients are examined "off medication", those with high tremor sub-scores likely have worse tremor during off states at night. Worse tremor during night off states have been shown to lead to increased sleep fragmentation, resulting from re-emergence of resting tremor during micro-arousals, body movements and sleep-state changes (mainly from NREM to REM sleep) [35]. Similarly, limb bradykinesia during night off states may cause difficulties in turning and adjusting the body position in bed, which are problems known to cause sleep fragmentation in PD patients [11, 36]. It has also been shown previously [8] that motor activity from tremor or motor fluctuations may disrupt the circadian system directly, since body movements impact the physiological cues used by this system.

Three larger studies that related motor disability to insomnia have been descriptive and none have analyzed motor UPDRS sub-scores, but they corroborate the present study's findings for positive associations of overall motor severity and insomnia symptoms. A large population-based French study (COPARK), reported cross-sectional results for 636 PD patients who responded to the PSQI questionnaire [18] with a mean PD duration similar to our study (6.3 years) and found higher motor UPDRS total scores in those with sleep disturbance (defined as PSQI score above 5, similar in content to the MOS-sleep insomnia measure adopted here), but the results reported were unadjusted for potential confounders, such as age, gender and PD duration. A population-based Norwegian cohort (n=231) also reported insomnia to be associated with higher motor UPDRS total scores, but estimates from this study were not formally statistically significant and, again, unadjusted for potential confounders [17]. In addition, this population had a higher PD duration at time of study (average of 9.8 years for patients with insomnia and 7.8 for those without insomnia). The third study, a hospital-based longitudinal Dutch study (PROPARK) assessed sleep quality in 412 patients (average PD duration of 10.6 years) with 27% reporting insomnia; in cross-sectional analyses, these patients exhibited higher total motor UPDRS scores, and more motor complications and fluctuations [15].

Similar to the results presented here, an international multicenter study of 423 PD patients (mean PD duration of 6.7 years) reported no association between total motor UPDRS scores and concurrent EDS [20, 37], but they did not report results for motor UPDRS sub-scores. In the PEG population-based patient cohort presented here, the only motor UPDRS sub-score associated with EDS was axial/gait/posture, which includes body bradykinesia; however, PIGD motor subtype was not associated with higher EDS symptoms. Only one other study, using a specialty clinic population from China, has reported positive associations between body bradykinesia scores and EDS [21]. Compared with this study's population, the Chinese sample had slightly shorter average PD duration (5.1 years) and scored higher on the total motor UPDRS.

Given these results, and as suggested previously by others [38], EDS, unlike insomnia, does not seem to be directly related to PD motor dysfunction resulting from primary nigrostriatal dopaminergic degeneration, but rather to features that suggest the degeneration of other neurotransmitter systems characteristic of more advanced disease [11]. For example, in post-mortem and brain imaging studies in clinical samples [39], EDS has been related to the degeneration of the alertness system, including hypocretin neurons in the hypothalamus, noradrenergic neurons in the Locus Coeruleus, and serotonergic neurons in the Dorsal Raphe Nuclei. In this study's analyses, accounting for GDS scores in models for body bradykinesia and EDS moved the estimates towards no association, supporting the hypothesis [40] that depression in PD is associated with slowness of movement (body bradykinesia) and EDS; a future study will further explore the association of depression and sleep problems in the PEG cohort.

Therapy with levodopa and dopamine agonists is another factor frequently associated with sleep problems in PD in clinical practice. In general, the PEG study population seems to be under-treated, as almost one in 10 patients were not under any PD medication or treatment such as DBS [41], which could be credited to the study's source population being communities of mostly rural counties with intense agricultural activity, and low average education and income, where access to health care resources is often limited. Pharmacologically, it has been proposed that levodopa can affect circadian rhythms directly in PD patients through mechanisms that uncouple circadian rhythm and sleep regulation [34], such as altering melatonin secretion and action. In this study, levodopa doses (LED≥500mg/day) were associated with both insomnia and EDS symptoms, in similar magnitude, while dopamine agonists doses (LED≥200mg/day) did not affect sleep symptoms. Previous studies reported conflicting results regarding the contribution of levodopa therapy to sleep problems. A population-based study from Norway and a hospital-based Dutch study [19, 23, 24] found slightly higher LED in PD patients with EDS cross-sectionally, but LED did not predict worsening of EDS over time. The Norwegian ParkWest population-based cohort [19] reported no association of total LED and EDS for patients within five years from PD diagnosis, but a higher proportion of patients used dopamine agonists, 57% compared with 38% in our PEG cohort. Dopamine agonists have been shown to improve sleep in previous trials of rotigotine [42, 43], and to be associated with EDS and sleep-attacks in some clinical-based epidemiological studies [44], but not others [45]. No population-based studies addressed specific associations of dopamine agonists and sleep symptoms, and the present study may not have been able to detect associations if they are present, since only 38% of the study sample took such drugs.

Axial/gait/posture motor features of PD can be less responsive to dopaminergic therapy than tremor signs, which influence type and doses of PD medication prescribed [18]. Thus, to verify if these motor features can explain the association between levodopa and EDS, the models were

further adjusted for axial/gait/posture motor sub-scores. Interestingly, this did not change the coefficients for levodopa (LED≥500mg), but the coefficient for the motor sub-score was no longer statistically significant. This may indicate that the association of axial/gait/posture sub-scores and EDS is mediated through levodopa doses.

As shown here and previously reported [15, 19, 20, 46], non-motor and autonomic symptoms affect sleep quality and are related to EDS. Some of these manifestations can directly induce sleep fragmentation, such as nocturia. Others have been associated with circadian rhythms disruption, such as autonomic dysfunction. In fact, this study shows a strong association of sleep problems with autonomic symptoms including light headedness, constipation, drooling, chewing/swallowing, and urinary symptoms. This may not be surprising, as outputs from the suprachiasmatic nucleus, a structure in the hypothalamus recognized as the central pacemaker responsible for the regulation of circadian rhythms, innervates autonomous nervous system structures. Through these outputs, many independent circadian oscillators operate in peripheral organs and, coupled with hormonal secretion (involving melatonin and cortisol), they synchronize physiological functions, resulting, for example, in circadian fluctuations in blood pressure, urinary excretion and gastrointestinal activity. Degeneration of circadian system structures that induce circadian disruption would, thus, be manifesting in peripheral organs as autonomic dysfunction.

In the sub-group of 156 patients assessed twice for sleep problems during follow-up, insomnia scores did not worsen substantially, even when assessing subgroups with different PD severity (by UPDRS, PD duration, LED, and non-motor symptoms). On the other hand, EDS scores seem to worsen over time, especially in patients with worse PD severity at first follow-up, i.e., they reached the highest sleep score averages at their second follow-up. This may suggest that insomnia manifests early in the disease course, possibly concomitantly with worsening in tremor symptoms, but this sleep feature does not worsen as PD progresses. Two previous smaller studies examined progression of sleep symptoms in PD and also found insomnia prevalence to slightly decrease over follow-up time (8 years), while EDS worsened with PD progression [17, 19]. Future larger population-based longitudinal cohort studies of PD are still necessary to address how circadian dysfunction progresses in PD clinical course.

Lack of temporality is a limitation of this study. The main results reported are cross-sectional, while the exposures and outcomes studied are part of a vicious cycle of deterioration during PD progression and influence each other longitudinally. The associations reported here refer to prevalent sleep symptoms at on average six years after PD diagnosis, and we do not know when these sleep problems started. Another potential limitation refers to the absence of objective measures of sleep quality and structure, since we relied solely on self-reported information. This is, however, a problem common to all population-based studies with large numbers of patients, due to feasibility constraints that do not support using objective sleep laboratory assessments, such as polysomnography. Unmeasured residual confounding is unavoidable in observational research, however, the regression models took into account explicit hypothesized causal structures [33], different from purely predictive modeling approaches of insomnia and EDS in PD. Important strengths of this study are the large number of subjects and the population-based approach to identify PD cases, which likely yields estimates that are more representative of all PD patients, than those based on very selected clinic-based patient samples.

5. Conclusions

In conclusion, this study provides epidemiological evidence that motor and non-motor dysfunction in PD is associated with insomnia and EDS symptoms, but specific features and level of severity affect these sleep symptoms differently. While motor severity measured by total UPDRS score and sub-scores of tremor, limb bradykinesia and motor complications mainly impact insomnia, EDS symptoms were related to axial/gait/posture motor features, which may indicate higher levodopa doses and/or more advanced disease. Future assessments of sleep problems in longitudinal population-based studies are needed to help improve patients' overall health-related quality of life.

Acknowledgments

Additional Materials

The following additional materials are uploaded at the page of this paper.
1. Figure S1: Proposed Directed Acyclic Graph (DAG) depicting hypothesized relation of factors considered in cross-sectional analyses. Arrows in purple represent the main potential causal relations we aimed at estimating. Variables in parenthesis are not measured. UPDRS-III= measure of motor dysfunction severity. EDS= excessive daytime sleepiness.
2. Figure S2: Correlations among PD-related and sleep variables considered in analyses.

Author Contributions

Jeff M Bronstein and Adrienne Keener conducted most of the clinical assessments of Parkinson's disease patients, at baseline and follow-up. Aline Duarte Folle conducted the analyses, with support from Kimberly Paul and Cynthia Kusters, and wrote the first draft of the paper, under supervision of Beate Ritz, who is responsible for the conception of the study. All authors contributed in discussing results and editing the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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