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Sleep Problems in Parkinson's Disease Patients from a Population-based Cohort in Central California

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Sleep Problems in Parkinson's Disease Patients from a Population-based Cohort in Central California

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by

Aline Duarte Folle

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ABSTRACT OF THE DISSERTATION

Sleep Problems in Parkinson's Disease Patients from a Population-based Cohort in Central California

by

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University of California, Los Angeles, 2019

Professor Beate Ritz, Chair

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world, and aging individuals are at greater risk for developing it. Though PD is better known by its motor manifestations of tremor at rest, bradykinesia, and rigidity, it also encompasses a variety of non-motor symptoms (NMS). These usually impact patients' quality of life at a similar or greater extent than the motor signs. NMS include autonomic disturbances (constipation, urinary and gastric problems), mood and neuropsychiatric symptoms (depression, anxiety, and apathy), and sleep disturbances. Sleep-related disorders are one of the most common NMS in PD, especially insomnia, excessive daytime sleepiness (EDS), and REM sleep behavior disorder (RBD). Because sleep problems are also highly prevalent in the general older adult population and constitute a public health problem, our aim was to investigate multiple clinical factors,

related and unrelated to PD, as potential causes or effects of self-reported sleep problems in Parkinson's disease patients from a population-based cohort in Central California.

We first analyzed the association of probable RBD features (pRBD), measured with a questionnaire, with PD motor and cognitive progression. With information from 716 patients at baseline, prevalence of pRBD was 21%. In adjusted Cox regression models among patients with a Postural Instability and Gait Dysfunction (PIGD) phenotype, those with pRBD progressed faster to a motor UPDRS ≥ 35 (HR= 1.9, 95% CI= 1.1; 3.3). All patients with pRBD progressed twice as fast to a MMSE score≤ 24 (HR= 2.0, 95% CI= 1.1; 3.7).

From 477 patients who completed at least one follow-up, we had information on the MOS-Sleep questionnaire to examine the cross-sectional associations of PD specific features with insomnia and EDS symptoms at an average of six years of PD duration. For 156 patients, information on a second measure was also available on average two years after the first. In adjusted linear regressions with standardized insomnia or EDS scores as outcomes (mean=0 and standard deviation=1), PIGD motor signs, worse autonomic symptoms, and complex non-motor symptoms (depression, anxiety, apathy, hallucinations and dopamine dysregulation syndrome) were associated with both scores. Yet motor UPDRS tremor sub-scores and motor complications were only associated with increase in insomnia scores, and levodopa dose was associated strongly with EDS score increase (β=0.04; 95% CI 0.01, 0.08) than with insomnia (β=0.03; 95% CI 0.00, 0.06).

We also examined the association of historic neuropsychiatric diagnoses and medication, and concurrent depression symptoms with prevalent insomnia and EDS at the same average of six years of PD duration. Average MOS-Sleep EDS score was 42.2± 23.7, and insomnia score was 30.5± 22.6 (range 0 – 100). In women, anxiety or depression diagnosis occurring 10+ years before PD contributed most strongly to insomnia scores, compared to those never diagnosed (mean difference: 13.8; 95% CI 5.5, 22.0). While in men, depression or anxiety diagnosed in prodromal or clinical stages of PD (<10 years before PD diagnosis) contributed to insomnia symptoms (8.0; 95% CI 1.8, 14.2) and to EDS (9.4; 95% CI 2.4, 16.3). Current depression treatment and symptoms were strongly associated with EDS in men more than women.

In longitudinal models, only those with lower motor or autonomic symptom scores at the first follow-up showed further increase in insomnia scores after two additional years. This suggests that there may be a saturation effect of how these PD features affect further worsening of insomnia symptoms over the course of PD. Mood symptoms (GDS scores) at the first sleep measure were not associated with worsening sleep symptoms over two years of follow-up.

Employing data from one of the largest population-based studies of PD, in which movement disorder specialists assessed patients, we confirmed evidence that pRBD features are a clinical marker for faster cognitive decline and possibly also motor progression in PD patients, the latter for patients with a PIGD subtype early in the disease. Although sleep problems in PD result from a complex interaction of lifestyle and clinical factors that can be PD-related or not, we estimated the contribution of some PD-related features to insomnia and EDS symptoms, showing that different PD features are associated with different sleep symptoms, providing insight into how

sleep symptoms change over time. We also indicate evidence that mood disorders diagnosis and symptoms contribute to prevalent insomnia and EDS symptoms in PD patients, with features differing in men and women.

The dissertation of Aline Duarte Folle is approved.

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TABLE OF CONTENTS

LIST OF TABLES ix
LIST OF FIGURES xi
ABBREVIATIONS AND ACRONYMS xii
ACKNOWLEDGEMENTS xiv
VITA xvii

1 Introduction 1
1.1 Parkinson's Disease 1
1.2 Sleep and General Regulation of Sleep-Wake Cycles 4
1.3 Circadian Rhythms and System 7
1.4 Circadian Disruption and Sleep Problems in PD 9

2 Clinical Progression in Parkinson's Disease with Features of REM Sleep Behavior Disorder: a Population-based Longitudinal Study 15
2.1 Abstract 15
2.2 Introduction 16
2.3 Methods 17
2.4 Results 21
2.5 Discussion 23
2.7 Tables and Figures 30
2.7 Supplementary material 36

3 Parkinson's Disease-Related Risk Factors for Insomnia and Excessive Daytime Sleepiness in a Population-based Study 45
3.1 Abstract 45
3.2 Introduction 46
3.3 Methods 48
3.4 Results 53
3.5 Discussion 56
3.6 Tables and Figures 63

4 Depression and Anxiety Affect Insomnia and Excessive Daytime Sleepiness in Community-based Parkinson's Disease Patients 73
4.1 Abstract 73
4.2 Introduction 74
4.3 Methods 76
4.4 Results 81
4.5 Discussion 85
4.6 Tables and Figures 91

5 Public Health Relevance and Expected Contributions 104

6 References 106

LIST OF TABLES

Table 2-1. Baseline distribution of PD patients' characteristics: overall and by pRBD status … 29

Table 2-2. Baseline and follow-up motor and non-motor outcomes by baseline pRBD status ……... 31

Table S2-1. Baseline distribution of PD patients' characteristics: overall and stratified by follow-up status ……... 37

Table S2-2. Annual rate of progression (mean change in scores per year of follow-up), overall and by pRBD status ……. 39

Table S2-3. Motor and non-motor outcomes scores, overall and differences by baseline pRBD status …… 40

Table S2-4. Hazard rate ratio estimates for motor and cognitive progression events comparing with pRBD to without pRBD1: sensitivity analyses ……...… 41

Table 3-1. Distribution of demographics, PD-related characteristics and MOS-Sleep scale scores for Insomnia and EDS, at first follow-up. PEG Study 2019 …… 63

Table 3-2. Linear regressions of insomnia and EDS scores on PD-related characteristics (cross-sectional), adjusted for sex, age and duration of Parkinson's disease in years. PEG Study 2019 ……... 65

Table 3-3. Linear mixed models: association of PD-related characteristics and change in sleep problems scores across two points (n=156 with follow-up). PEG Study 2019 ……..... 67

Table 4-1. Distribution of characteristics for PD patients at first sleep measure, and Insomnia and EDS scores by patients' characteristics. PEG Study 2019 …….....… 91

Table 4-2. Linear regressions of insomnia scores on neuropsychiatric measures, adjusted for gender, age, duration of Parkinson's disease in years, and UPDRS-III (motor signs severity). PEG Study 2019 ……... 93

Table 4-3. Linear regressions of EDS scores on neuropsychiatric measures, adjusted for gender, age, duration of Parkinson's disease in years, and UPDRS-III (motor signs severity). PEG Study 2019 …….. 96

Table 4-4. Linear mixed models: association of PD-related characteristics and change in sleep problems scores across two points (n=156 with two sleep measurements). PEG Study 2019 … 98

Table S4-1. Linear mixed models: association of depression symptoms (GDS) and change in sleep problems scores across two points on average 2.2 years apart (n=156 with two sleep measurements). Sensitivity analysis with different GDS cut-offs, and adjustment variables. PEG Study 2019 …….. 103

LIST OF FIGURES

Figure 2-1. Flowchart of Parkinson's Environment and Genes (PEG) Study, first and second cohorts, baseline and follow-ups. …… 33

Figure 2-2. Hazard rate ratios (HR) estimated for clinical progression events and pRBD. …… 34

Figure S2-1. Screening questionnaire used to measure features of RBD in adult life. …… 42

Figure S2-2. Proposed Directed Acyclic Graph depicting hypothesized relation of factors considered in analyzes. …… 43

Figure 3-1. Scatterplot of standardized sleep scores (mean 0, SD 1) by PD characteristics stratified by gender. Including best fit linear correlation line and Pearson correlation coefficients and p-values. PEG Study 2019. ……... 68

Figure S3-1. Proposed Directed Acyclic Graph (DAG) depicting hypothesized relation of factors considered in cross-sectional analyzes (arrows in purple). …… 70

Figure S3-2. Correlations among PD-related and sleep variables considered in analyses. PEG study 2019. ……..……. 71

Figure S3-3. Plots of predicted values from linear mixed models fixed-effects coefficients depicted in Table 3-3. PEG Study 2019. …… 72

Figure 4-1. Insomnia and EDS mean scores by other sleep characteristics. RBD= REM Sleep Behavior disorder. PEG Study 2019. ……... 99

Figure 4-2. Insomnia predicted mean scores by co-morbidities and lifestyle characteristics, adjusted for age, PD duration, gender and ethnicity. PEG Study 2019. …… 100

Figure 4-3. Scatterplot of sleep scores by health-related quality of life measured by SF-36 scores, stratified by Geriatric Depression Scale (GDS) <7 and 7+. PEG Study 2019. …….. 101

Figure 4-4. Scatterplot of sleep scores by Geriatric Depression Scale (GDS) stratified by concurrent medication use and gender. Including best fit linear correlation line and Pearson correlation coefficients and p-values. PEG Study 2019. ……...… 102

ABBREVIATIONS AND ACRONYMS

DA	Dopamine
DBS	Deep Brain Stimulation
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Scale
EEG	Electroencephalogram
GDS	Geriatric Depression Scale
MMSE	Mini-mental State Examination
MOS	Medical Outcomes Study
MOS-Sleep	Medical Outcomes Study Sleep Scale
NMS	Non-motor symptoms
NREM	Non-Rapid eye movement
PD	Parkinson's disease
PEG	Parkinson's disease, Environment and Genes
pRBD	Probable REM Sleep Behavior Disorder
PSQI	Pittsburgh Sleep Quality Index
PDSS	Parkinson's Disease Sleep Scale
REM	Rapid eye movement

RBD	REM Sleep Behavior Disorder
UPDRS	Unified Parkinson's Disease Rating Scale

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1 Introduction

1.1 Parkinson's Disease

Parkinson's disease (PD) was systematized as a clinical entity in modern medicine by Dr. James Parkinson in 1817 (Parkinson, 2002). PD is the second most frequent neurodegenerative disorder, after Alzheimer's disease (Pringsheim, Jette, Frolkis, & Steeves, 2014), with a worldwide prevalence ranging from 41 to 1,903 per 100,000, in individuals 40 to 49 years and over 80 years of age, respectively, according to a meta-analysis published in 2014 (Pringsheim et al., 2014). This same study found the prevalence to be greater in Europe, North America and South America compared to Africa and Asia. A study in California reported an overall annualized age and gender adjusted incidence rate for PD of 13.4 per 100,000, rapidly increasing over the age of 60, to 38.8 (60-69), 107.2 (70-79) and 119.0 (80-89) and higher in men than women (Van Den Eeden et al., 2003).

PD etiology is multifactorial, with aging being the strongest risk factor for incidence. Other factors identified include male sex and some environmental exposures such as pesticides, head injury, rural residence, farming occupations, and well-water drinking (Kalia & Lang, 2015). Genetic risk factors have started to be better understood since the beginning of the 21st century and the main Mendelian genes found to be associated with dominantly or recessively inherited familial PD include: GBA, SNCA, LRRK2, Parkin, PINK1, DJ1. Recently, GWAS studies have allowed more detailed understanding of PD incidence, progression and characteristics (Edwards et al., 2010; Paul, Schulz, Bronstein, Lill, & Ritz, 2018).

The pathological hallmarks in PD are death of dopaminergic neurons in the substantia nigra pars compacta (in the basal ganglia) and widespread Lewy pathology (Kalia & Lang, 2015). Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain and is involved in regulation of a number of central and peripheral nervous functions, such as locomotor activity, cognition, emotion, reinforcement, reward, endocrine regulation, cardiovascular and renal function, and gastrointestinal mobility (Missale, Nash, Robinson, Jaber, & Caron, 1998). Five types of DA receptors have been identified from animal studies (D1-D5), of which D1, D2 and D3 are known to be associated with motor activity (Missale et al., 1998).

Lewy pathology corresponds to deposition of insoluble aggregates formed upon abnormal folding of the protein α-synuclein, called Lewy bodies and Lewy neurites, found within the neuronal bodies and processes in the brain, spinal cord and peripheral nervous system. These cellular inclusions have been described for the first time in 1912 and in the 1990s, α-synuclein was identified as their main component; its aggregation was shown to be a central pathological marker for a group of diseases named α-synucleinopathies, including PD, dementia with Lewy bodies, and multiple system atrophy (Goedert, Spillantini, Del Tredici, & Braak, 2013). According to a widely accepted hypothesis (Braak et al., 2003), this pathological marker spreads from peripheral to central nervous system regions as the disease progresses, correlating with increasing neurodegeneration and symptomatology. More recently, other pathological markers and mechanisms have been proposed for PD neurodegeneration such as neurotoxicity due to other conformations of α-synuclein (oligomers) and neuroinflammation.

Besides dopaminergic neurodegeneration in central structures, it is also known that neuronal loss in PD occurs in others neurotransmitter circuits and structures, including serotonergic, noradrenergic and cholinergic. Because of its diverse pathological characteristics, PD comprises a wide range of clinical presentations. Motor signs are the most obvious and were part of the previous denomination of PD, Shaking Palsy (Parkinson, 2002); the classical ones are rest tremor, rigidity and bradykinesia, and constitute part of the currently established diagnostic criteria. Other clinical features, known as non-motor symptoms (NMS) (Pfeiffer, 2016), are also common and have been described since Dr. James Parkinson's classical essay published in 1817 (Parkinson, 2002), detailing the clinical presentation of PD.

NMS consist of sensorial, sleep, gastrointestinal, mood and other neuropsychiatric disturbances, experienced to different degrees and in various combinations by all patients with PD. Some studies have shown that NMS predict quality of life more strongly than motor symptoms (Y. Wu et al., 2016; Ying Wu et al., 2014). These symptoms have been attributed to neurodegeneration in non-motor structures and they may even begin before the onset of classical motor symptoms, according to Braak hypothesis (Braak et al., 2003). Some NMS are also considered markers for PD onset prior to the traditional diagnosis based on motor symptoms, and recently , attempts have been made to classify sub-types of PD based on these features (Sauerbier, Jenner, Todorova, & Chaudhuri, 2016).

PD research has focused on trying to identify risk or preventive factors for PD to potentially develop disease-modifying agents, capable of slowing, stopping or reversing neurodegeneration, since the drugs and therapies currently available are only symptomatic (Kalia, Kalia, & Lang,

2015). Current available pharmacological treatments of motor symptoms aim at enhancing intracerebral DA concentrations and stimulating DA receptors. The main classes of drugs used for these purposes are levodopa, dopamine agonists, monoamine oxidase type B inhibitors, and amantadine (Kalia & Lang, 2015). Some important adverse events associated with treatment with DA agonists and with long-term levodopa use include motor fluctuations and dyskinesia, nausea, daytime somnolence, edema, impulse control disorders and psychosis or hallucinations. New drugs and formulations have been tested to address those side effects. Deep brain stimulation (DBS) is now a well-established surgical treatment for those suffering from motor fluctuations or dyskinesia from levodopa use, and it has been shown to improve DA treatment (L-dopa or agonist) responsive motor symptoms even in advanced stages, and potentially affect some non-motor features, including sleep-related symptoms, and behavioral problems (Mcintyre & Anderson, 2016).

Pharmacological treatment of NMS may be more challenging, since many of them result or are worsened by concomitant disturbances in non-dopaminergic neurotransmitter systems, hence they often do not respond to levodopa therapy. Some drugs with action on other neurotransmitter circuits are frequently used to address these symptoms, such as cholinesterase inhibitors, antidepressants, benzodiazepines and atypical antipsychotics (Kalia & Lang, 2015; Zis, Erro, Walton, Sauerbier, & Chaudhuri, 2015)

1.2 Sleep and General Regulation of Sleep-Wake Cycles

Sleep and wakefulness reflect two distinct behavior states. During waking an animal exhibits voluntary motor activation and is responsive to internal and external stimuli (Scammell,

Arrigoni, & Lipton, 2017). Sleep is a state marked by fading of consciousness in humans, but obviously different from other states with loss of consciousness such as coma and anesthesia. This state had been assessed mostly by polysomnography, a technique including electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG). The output of these assessments have been used to describe and define sleep macro structure into stages, and to, more recently, better characterize sleep micro structure.

As explained in detail by Bah et al in a review published in 2019 (Bah, Goodman, & Iliff, 2019), sleep states are categorized by the American Academy of Sleep Medicine into three non-rapid eye movement (NREM) sleep stages (N1, N2, N3), and REM sleep (R stage). Stage N1 sleep, called transitional or light sleep, is the first to occur following wakefulness, it is very short, lasting 1 to 7 minutes, and is characterized by low-voltage and fast EEG activity, including theta (4-8 Hz) activity and low-amplitude beta (> 13 Hz) activity, coupled with slow eye movements and variable EMG amplitude. In addition, stage N1 may show minimal alpha (8-13 Hz) and delta (0-4 Hz) activity, as well as presence of large amplitude waveforms called K complexes, and of sleep spindles (11-16 Hz bursts). Stage N2, called intermediate sleep, is characterized predominantly by theta (4-8 Hz) activity and occasional bursts of faster activity, coupled with no eye movement and a tonically low EMG activity. This stage lasts about 20 minutes, and it is accompanied by progressive diminution of peripheral physiological and metabolic functions. Stage N3 sleep, called deep or slow wave sleep, has the highest threshold for arousal, it is characterized by high-amplitude slow waves dominated by delta (0-4 Hz) activity as well as further reductions in muscle activity.

REM sleep, known as paradoxical or active sleep, is characterized by low-amplitude, mixed-frequency EEG theta (4-8 Hz) intermixed with alpha (8-13 Hz) waves, coupled with pronounced rapid eye movements and muscle atonia. REM sleep is associated with dreaming and greater physiological and metabolic activity, with increase and intermittent fluctuations in blood pressure and heart rate, irregular respiration, and increase in brain oxygen consumption. Healthy adults go sequentially from stage N1, N2, N3, and REM sleep to complete a sleep cycle over the course of 60 to 120 minutes, with several sleep cycles occurring throughout the night. The proportion of time in each state vary during the night, with more time in REM sleep in later cycles (Bah et al., 2019).

Regulation of sleep-wake cycles is coordinated by two interchanged processes which interact to determine sleep onset and cessation, as well as the stability of waking neurocognitive function (Bah et al., 2019). The processes are called S, for the homeostatic sleep drive, and C, for the circadian sleep drive. Process C establishes sleep and wake into discrete periods reflecting daily rhythms in physiological function and behavior entrained by the environmental light/dark cycle. The mechanism of switching of the brain between stable arousal states is known as the flip-flop switch, and is accomplished through opposing inhibitory actions of sleep-promoting and wake-promoting regions on one another.

Wakefulness is initiated and maintained through an activated cerebral cortex via two factors, which arise from input from multiple activating systems via mechanisms of the ascending

reticular activating system[1], and the resistance of Process S by Process C. When the circadian drive for arousal diminishes and Process S increases over a threshold, it takes over Process C and sleep is triggered. This process is mainly driven by adenosine, which acts as a homeostatic regulator for sleep need. Adenosine acts both through inhibition of wake-promoting brain areas, and exciting sleep-promoting brain regions, such as the anterior hypothalamus and the ventrolateral pre-optic nucleus. specifically, adenosine acts to disinhibit gamma-aminobutyric acid (GABA) inputs exciting neurons in the ventrolateral preoptic nucleous, which inhibit arousal systems setting the thalamocortical network into a progressive state of synchronization, initiated by synchronous discharge of the thalamic reticular nucleus. This promotes sleep spindle generation and the initiation of sleep stage N1 (Fifel, 2017).

1.3 Circadian Rhythms and System

Circadian rhythms are biological cycles of physiological and behavioral regulated by endogenous processes with periodicity of approximately 24 hours that persist without environmental cues (Fifel, 2017; French & Muthusamy, 2016; Mantovani, Smith, Gordon, & O'Sullivan, 2018). These rhythms allow organisms to predict daily events and organize biology, to cope with evolutionary environmental constraints. They are generated and maintained as a result of coherent synchronization between hierarchically interrelated compartments of the circadian network. The central peacemaker of this network is the suprachiasmatic nuclei (SCN),

[1] The ascending reticular activating system works to activate cerebral forebrain structures mainly via two major pathways, the first includes projections from serotonin neurons of the dorsal raphe nuclei, noradrenaline or norepinephrine neurons of the locus coeruleus, and DA neurons of the substantia nigra and ventral tegmental area. The second pathway includes projections from glutamate, hypocretin, and the histaminergic tuberomammillary nucleus of the posterior hypothalamus, midline-intralaminar thalamus, and the cholinergic nucleus basalis neurons (French & Muthusamy, 2016).

which consists of bilateral nuclei with approximately 10,000 neurons located in hypothalamus just above the optic chiasma, and is the focal point for generation of circadian rhythms that regulates proper timing of all physiologic functions. The SCN aligns this timing to the 24-hour light/dark cycle in the natural environment, a process known as photo-entrainment. This process is made possible with photic inputs from the retina through a monosynaptic pathway called the retinohypothalamic tract, which originates from a small population of photosensitive melanopsin-expressing ganglion cells (ipRGCs) in the retina. After integrating these photic inputs with other inputs from neuronal and humoral signals, and from other indirect systemic functions, such as temperature, metabolism, food intake and fast periods, the SCN then also uses neuronal and humoral signals to transduce its endogenous rhythmic signal to many central and peripheral regions tissues to regulate independent circadian oscillators throughout the body (Mantovani et al., 2018).

This is made possible through SCN outputs which massively innervate hypothalamic regions including via the hypothalamic-pituitary adrenal axis, and the autonomic nervous system. Melatonin plays a major role in the regulation and synchronization of circadian rhythms, its production occurs during the dark phase and is suppressed by light, thus it is considered an endogenous signal for darkness. The SCN also receives feedback from the pineal gland, which regulates melatonin production and secretion through melatonin receptors located at a major site of the SCN (Fifel, 2017).

At the molecular level, circadian rhythm regulation occurs through an autonomous genetic network with interconnected negative and positive transcription-translation feedback loops

(Scammell et al., 2017). The mechanism basically consists of two interconnected, regulatory feedback loops; the first, regulates the transcription of PER 1,2,3 (Period) and CRY 1,2 (Cryptochrome), during the day, by two transcriptional activators, BMAL1 and CLOCK (which stands for Circadian Locomotor Output Cycles Kaput, also called NPAS2). BMAL1-CLOCK form heterodimers in the cytoplasm and enter the nucleus to bind to the promoters of PER and CRY genes. Proteins PER and CRY, in turn, also heterodimerize in a complex that translocates to the nucleus and interacts with the CLOCK-BMAL1 complex to inhibit its own transcription when their activation levels decline, forming the arm of the negative feedback loop. During the night, the PER-CRY complex is degraded, and CLOCK-BMAL1 can then start a new cycle of transcription.

An additional interlocking loop regulates the expression of the BMAL1 gene. In the nucleus CLOCK-BMAL1 heterodimers also bind to the promoters of genes that encode the retinoic acid-related orphan nuclear receptors: Rev-erb! and Ror!, which respectively suppresses and activates BMAL1 expression. As a consequence, oscillations of BMAL1 and Ror!/Rev-erb! are imbalanced, and if activation dominates expression, BMAL1 protein is produced and forms heterodimers in the cytoplasm with CLOCK. These heterodimers then enter the nucleus and initiate the next cycle of gene activation of both loops. While this mechanism is the most well elucidated to regulate circadian rhythms at the molecular level, there are other candidate clock components which have also been shown to influence the circadian clock (Scammell et al., 2017).

1.4 Circadian Disruption and Sleep Problems in PD

Sleep and circadian disturbances occur in the majority of PD patients, most likely due to a combination of PD underlying pathophysiology and clinical features related to PD and to aging, which are interconnected in a vicious cycle of circadian disruption, worsening in sleep, and PD manifestations.

Because of constrains related to the measurement methods availability, cost, and easiness of application, studies of sleep with objective assessments in PD are clinical based and usually small. In general, it has been reported that PD patients experience reduced total sleep duration, with increased number of awakenings and wakefulness after sleep onset, resulting in a disturbance called sleep fragmentation. Increased arousals are also common and may lead to excessive daytime sleepiness(French & Muthusamy, 2016). Some specific alterations in macrostructure of sleep reported in previous studies of PD patients are increased NREM sleep stage 1 and reduced REM sleep and non-REM sleep stages 3 and 4, with general difficulty performing transitions between stable sleep stages (bradysomnia). In sleep microstructure, probable alterations in PD patients include for instance, lower density of sleep spindles in NREM stages.

Studies in animals, postmortem in human brain tissues, or using neuroimaging have shown how PD-related damage and cell loss probably occur in several brain structures related to circadian function and sleep in general, affecting several neurotransmitter systems. As detailed in the review paper by French et al 2016 (French & Muthusamy, 2016), some of these systems and structures include, for example: the dopaminergic ventral tegmental area, serotonergic dorsal

raphe nucleous, noradrenergic locus coeruleus and vagus nerve, cholinergic hippocampus and pedunculopontine nucleus, and hypocretinergic neurons in the lateral cerebral ventricle.

Sleep disorders have been classified for research and diagnostic purposes by the International Classification of Sleep Disorders (ICSD), organized by international sleep disorder societies, and published for the first time in 1990 (Thorpy, 2012). The current version, ICSD-3 (ICSD-3, 2014), recognizes 81 major sleep disorders in eight categories: insomnias, sleep-related breathing disorders, hypersomnias of central origin, circadian rhythm sleep disorders, parasomnias and sleep-related movement disorders.

Sleep problems are one of the most common non-motor symptoms found in PD, with an estimated prevalence of 10 to 95%, depending on the problem type and disease stage (Iranzo, 2016). Besides risk factors associated with sleep problems in the general population, PD patients are subject to additional risk factors including those relating to direct impact of neurodegeneration on sleep and circadian functions, as discussed, and PD clinical features that may disrupt these functions through other mechanisms. These include for instance, nocturnal motor disturbances, such as re-emergence of tremor during sleep stages transitions, hypokinesia resulting in difficulty turning in bed during sleep, non-motor symptoms such as mood disorders and nocturia, treatment with levodopa, dopamine agonists, and other psychoactive medications drugs (Roychowdhury & Forsyth, 2012). Sleep problems have been shown to strongly predict quality of life and to be associated with worse functionality and dementia in PD (Chahine, Amara, & Videnovic, 2016). The most common sleep disorders in PD are: excessive daytime sleepiness (EDS), insomnia, rapid eye movement sleep behavior disorder (RBD), restless legs

syndrome (RLS) and periodic limb movements, and obstructive sleep apnea (OSA) (Hirata, Högl, Tan, & Videnovic, 2015; Lima, 2013; Roychowdhury & Forsyth, 2012).

Insomnia is characterized by difficulty in initiating and/or maintaining sleep and by poor quality of sleep, symptoms that are found in up to 80% of PD patients in some studies (Schrempf, Brandt, Storch, & Reichmann, 2014). Insomnia can be primary (intrinsic and extrinsic) or secondary to other disorders and the diagnosis is usually made based on clinical history (Thorpy, 2012). Primary insomnia is classified under both the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V). Insomnia can be assessed objectively in research using actigraphy measures with sleep diaries, while questionnaires have been validated to assess it subjectively (Högl et al., 2010; Schrempf et al., 2014). The main pathological and clinical factors found in previous studies to be associated with insomnia symptoms in PD are: neurodegeneration of sleep-related circuits, severity of motor symptoms, and other non-motor symptoms, such as restless legs syndrome, depression, and nocturia, due to autonomic system dysfunction (Chahine, Amara, et al., 2016).

Daytime sleepiness is defined as the "inability to stay alert and awake during the major waking episodes of the day, resulting in unintended lapses into sleep" (Thorpy, 2012). In the ICSD-3 and DSM-V, it is considered a symptom within the diagnostic category of the hypersomnia disorders. Excessive daytime sleepiness (EDS) is a frequently reported and distressful sleep-related symptom found in all phases of PD, including extreme and less common sleep attacks with sudden onset, similar to narcolepsy. Factors previously reported to be associated with EDS in PD include: neurodegeneration, dopaminergic and other medication (MAO-B inhibitors,

antidepressants and benzodiazepines), other NMS such as depression, insomnia and autonomic dysfunction. EDS can be assessed objectively in research with the multiple sleep latency test (MSLT), the maintenance of wakefulness test or the pupillographic sleepiness test (Schrempf et al., 2014), while questionnaires have also been validated to assess EDS subjectively (Chahine, Amara, et al., 2016).

REM sleep behavior disorder (RBD) is considered a parasomnia (events that accompany sleep), characterized by abnormal movements and behaviors, including dream enactment. RBD has been found to be associated with the degeneration of lower brainstem nuclei and to have strong prognostic value for PD and other synucleinopathies. It is estimated that up to 80% of patients with RBD are diagnosed with a neurodegenerative disorder after a mean interval of 14 years (Sixel-Döring, Trautmann, Mollenhauer, & Trenkwalder, 2014). The gold-standard for diagnosis of definite RBD is the polysomnography assessment, used as an objective measure in some clinical and epidemiological studies. Subjective assessments include questionnaires validated for use in research, but with a focus on potential application in clinical practice and, such as the Mayo Sleep Questionnaire and the RBD screening questionnaire (Högl et al., 2010; McCarter & Howell, 2016). These questionnaires yield the diagnosis of probable RBD (pRBD), in contrast to the definite diagnosis obtained with gold standard assessment with polysomnography. In studies of PD, prevalence of RBD problem has been found to be associated with older age, male sex, non-tremor dominant motor phenotype, falls, and depression (Boot et al., 2012).

Pharmacological treatment of RBD and insomnia in PD usually includes use of clonazepam, other benzodiazepines, gabapentin, and melatonin (Iranzo, 2016). While EDS in PD is rarely

treated pharmacologically, some pharmacological interventions that have been studied include modafinil and caffeine (Rodrigues, Caldas, & Ferreira, 2016).

Publications on risk factors and consequences of non-motor symptoms in PD, including sleep, have grown considerably in the last decade, but most of those analyses are from clinical-based studies with small samples of PD cases; there are still few publications about sleep from population-based studies in PD. Moreover, there are no such published data from studies conducted in the United States. More analyses from population-based studies assessing sleep in PD are necessary to keep elucidating symptoms' prevalence, incidence, risk factors and impact on disease progression. This knowledge can potentially contribute to the design of future studies and interventions aimed at ameliorating symptoms and PD progression, consequently improving clinical care and PD patients' quality of life.

2 Clinical Progression in Parkinson's Disease with Features of REM Sleep Behavior Disorder: a Population-based Longitudinal Study

2.1 Abstract

Introduction: Rapid Eye Movement (REM) sleep behavior disorder (RBD) is characterized by dream enactment and is associated with incidence of neurodegenerative disorders, especially Parkinson's disease (PD). Whether PD with RBD constitutes a distinct subtype with unique progression is unknown. Here, we investigated motor and cognitive symptom progression in patients with self-reported RBD features in adult life.

Methods: We screened for RBD in a cohort of 776 PD patients whom we ascertained using a population-based strategy. Among participants with at least one follow-up (60%), we compared those with and without probable RBD (pRBD) estimating hazard rate ratios for progression events UPDRS-III≥ 35 and MMSE≤ 24.

Results: Prevalence of pRBD at baseline was 21%. In adjusted Cox regression models among patients with a Postural Instability and Gait Dysfunction (PIGD) phenotype, those with pRBD progressed faster to a UPDRS-III≥ 35 (HR= 1.92, 95% CI= 1.12; 3.27). Also, all patients with pRBD progressed twice as fast to a MMSE score≤ 24 (HR= 2.04, 95% CI= 1.13; 3.69). In sensitivity analyses, using alternative definition of pRBD and accounting for bias due to loss to follow-up results remained similar.

Discussion: Employing data from one of the largest population-based studies of PD, in which movement disorder specialists assessed patients, we confirm evidence that pRBD features are a clinical marker for faster cognitive decline and possibly also motor progression in PD patients, the latter for patients with a PIGD subtype early in disease.

2.2 Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dream enactment, usually associated with dreams of violent content, and classified according to the International Classification of Sleep Disorders (ICSD-2) as a parasomnia, an event accompanying sleep, instead of a sleep disorder (Thorpy, 2012). RBD occurs due to motor activity during REM sleep resulting from transient loss of muscle atonia normally present during this sleep stage, sometimes resulting in injuries to the patient and/or bed partners. The disorder is considered rare, with a prevalence of less than 1% in general population (Fraigne, Torontali, Snow, & Peever, 2015), but with much higher prevalence in those afflicted by neurodegenerative diseases known as synucleinopathies, including Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and Multiple Systems Atrophy (MSA) (Ronald B Postuma, Bertrand, et al., 2012).

Population-based studies estimated the prevalence of RBD symptoms in PD as 15% (Gjerstad, Boeve, Wentzel-Larsen, Aarsland, & Larsen, 2008), while a meta-analysis including different study types estimated a 24% prevalence (J. Zhang, Xu, & Liu, 2017). Characteristics associated with RBD in previous PD studies include male sex, older age, longer disease duration, and greater motor severity (R. Zhu, Xie, Hu, & Wang, 2017). Attention to RBD has grown as it has become known for its link to neurodegenerative pathology (McKenna & Peever, 2017) and as a prodromal marker of Parkinsonism. About 75% of those suffering from RBD develop PD or a Parkinsonism within about 10 years (Iranzo et al., 2014; Jozwiak et al., 2017). Furthermore, it has been suggested that PD presenting with RBD symptoms may constitute a distinct PD

subtype, with features such as autonomic dysfunction, hallucinations, more axial symptoms, and faster cognitive decline (Fereshtehnejad et al., 2015; Ronald B Postuma, Bertrand, et al., 2012).

Elucidating whether PD with RBD indeed constitutes a distinct phenotype with a unique etiology and disease course or is indistinguishable from idiopathic PD without RBD is crucial for upcoming neuroprotective trials and clinical care. To date, most studies on PD with RBD enrolled few subjects, selected participants from tertiary clinical settings, and/or relied on cross-sectional designs. Since prospective and population-based epidemiological studies may help us gain better insights into the role of RBD in PD, we investigated how self-reported RBD-like features manifesting in adult life are related to motor and cognitive symptom progression in a large population-based PD patient cohort.

2.3 Methods

Research Ethics

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.

Study design

PD patients enrolled in the Parkinson's Environment and Genes Study (PEG), were identified in two independent waves (PEG 1 & PEG 2), from the population of three California counties. In the first wave, new onset PD cases (≤3 years from diagnosis) in the region were identified by contacting health professionals, and in the second wave, PD cases (≤5 years from diagnosis)

were identified through a population-based PD registry. Eligible cases had lived in California five years at minimum and agreed to participate. Baseline neurologic exams occurred between 2001 and 2007 (PEG 1), and 2011-2017 (PEG 2). PEG 1 participants were seen up to four times during follow-up thus far, on average 3.2 years apart. For PEG 2, there has only been one follow-up thus far, on average 3.3 years after baseline. Figure 3-1 shows flowchart for baseline recruitment and follow-ups.

Data collected

At baseline and each follow-up, UCLA movement disorder specialists confirmed a diagnosis of idiopathic PD and evaluated motor features using the Unified Parkinson's Disease Rating Scale (UPDRS parts I, III and IV) and Hoehn and Yahr staging (HY). At each time point, over 80% of the participants were evaluated in an 'off' (≥ 12 hours) medication state. For those 'on', we added a correction factor to their UPDRS-III total score, equal to the mean difference of 'off' and 'on' scores in all patients. We also used the average of the whole sample to impute missing items (mainly due to disability impeding evaluation of specific items such as 'arise from chair'). We adopted the MDS version of the UPDRS-III in 2016, thus, scores derived from this scale were corrected by subtracting six points.

At baseline, participants were screened for RBD (Figure S3-1) answering four questions about nighttime sleep as an adult: 1- acting out dreams, 2- talking/yelling/screaming, 3- walking, 4- aggressive behaviors (1- definitely happened, 2- may have happened but not sure, 3- unlikely to have happened, 4- I don't know if happened). We defined probable presence of RBD features (pRBD) based on questions # 1 and 4 only, as an answer of *definitely happened* to at least one

with the other being at least *may have happened*, i.e. they were certain that they had acted out dreams or shown aggressive behaviors during sleep, and did not negate the possibility of the other action completely. Trained researcher assistants also collected data on demographics, lifestyle and environmental exposures, medical history, and applied standardized instruments: UPDRS patient questionnaire (parts IB+II), Mini-Mental State Examination (MMSE), and Geriatric Depression Scale (GDS) (Hoops et al., 2009). UPDRS-I and II were only administered at follow-up. From these interview data, we calculated Levodopa Equivalent Dose (LED), as previously described (Keener, Paul, Folle, Bronstein, & Ritz, 2018).

PD clinical progression was defined in terms of time to a motor and a non-motor outcome. A UPDRS-III score≥ 35 (higher score represents worse motor function) was chosen as a meaningful threshold for motor progression because it represents, on average (Shulman, 2010), motor progression to a stage where patients start presenting some dependency for functional activities, equivalent to a HY stage 3 and to 60% in Schwab and England scale. For cognitive decline, a MMSE score≤ 24 (lower scores represent worse cognition) was chosen as the threshold, as previously done (Keener et al., 2018). Time to event was defined as the interval in years from baseline (time=0) to the first time the event was recorded at a follow-up visit; those with the event at baseline were excluded from progression analyses.

Using items scores from UPDRS-III at baseline, we classified participants into motor subtypes of Postural Instability and Gait Dysfunction (PIGD), Tremor Dominant (TD), or Indeterminate (IND), as previously described (Stebbins et al., 2013). Summing up specific items from UPDRS-

III, we calculated subscores of bradykinesia, rigidity, tremor, axial (Gigante et al., 2015), and PIGD features.

Statistical analysis

Analyses were conducted in statistical software package SAS (SAS Institute) version 9.4, and forest plot figure was generated in R (package forestplot). Cross-sectional comparisons of clinical and lifestyle characteristics between groups with and without pRBD were tested using t-tests or linear regressions for continuous characteristics, and chi-square or logistic regressions (ordinal logistic regression for more than two categories) for categorical.

We used Cox proportional hazards regression models to obtain hazard rate ratios and 95% confidence intervals (CI) comparing clinical progression between groups with and without pRBD. We assessed the proportional hazards assumption plotting product-limit survival curves for each outcome and time variables, stratified by pRBD, confirming that hazard rates were proportional between groups. All regression models were fitted by maximum likelihood methods.

We selected covariates for adjustment in regression models based on assumptions derived from previous knowledge and encoded using Directed Acyclic Graph (DAG) (Figure S3-2) methodology (Hernán, Hernández-Díaz, & Robins, 2004). Baseline characteristics assumed to be confounders were: sex, age at PD diagnosis, PD duration, ethnicity (minority yes/no), baseline wave (PEG1/2), smoking in pack-years, and years of education (for cognition) and comorbidities (note: comorbidities (high blood pressure, diabetes type 2, anxiety, and depression) did not

change estimates under these scenarios, and we did not include these to avoid generating spare data strata). The models were also stratified by motor subtypes.

To account for lack of information about outcomes on the 44% of participants not seen for follow-up, we used Inverse Probability of Censoring Weighting (IPCW) (Hernán et al., 2004), generating weights conditional on presumed determinants of loss to follow-up (Supplemental Methods, and Table S2-4). Weights were applied to Cox models using robust standard errors estimation. In sensitivity analyses, we defined pRBD only by an answer '*definitely happened'* to Question #1- acting out dreams (Table S2-4).

2.4 Results

Overall prevalence of pRBD in adult life was 21% (15% in PEG1 and 25% in PEG2), shown in Table 2-1. Fewer pRBD participants were females (24 vs. 40%) and more self-reported diagnoses of myocardial infarction, anxiety, and depression before baseline. Patients reporting pRBD had slightly lower mean MMSE scores, longer average disease duration, and a trend for a higher LED (p=0.06). Average time from baseline to first follow-up was 3.4 (SD= 1.6, min-max=0.7-15) years overall and by pRBD status.

Of the 44% (362 out of 832) missing follow-up information, most had died or were severely debilitated at our last attempt of contact. Those without follow-up information had a similar prevalence of pRBD at baseline, but were older, had longer PD duration, exhibited a PIGD subtype, and had more comorbidities (Table S2-1).

Table 2-2 shows cross-sectional associations of pRBD with motor and non-motor outcomes. At baseline, motor signs (UPDRS-III total score and subscores, and HY≥3) were similar in both groups, while at first follow-up (average PD duration of 6.1± 2.8 years), pRBD was associated with slightly higher bradykinesia and axial UPDRS-III subscores. MMSE scores were lower at both times for those with pRBD, while GDS scores were similar. At first follow-up, non-motor symptoms measured by UPDRS-I/II, were worse in pRBD, specifically, patients reported more hallucinations.

Of participants with at least one follow-up motor evaluation (n=416), a total of 115 (30%) developed the event UPDRS-III≥ 35 (Figure 3-2) and the incidence was higher in those with pRBD (33%). In Cox models adjusted for potential confounders, pRBD PD patients progressed faster to a UPDRS-III≥ 35 than those without pRBD (HR= 1.48), but the HR estimate was not formally statistically significant at alpha=0.05 (p=0.08, 95% CI= 0.95; 2.32). When stratifying by motor phenotypes, only among PIGD patients pRBD was a risk factor for faster progression to a UPDRS-III≥ 35 (HR= 1.92, 95% CI= 1.12; 3.27).

The group with pRBD also had a greater incidence for a MMSE≤ 24 during follow-up (19% compared to 13% in without pRBD). The hazard rate for progression to this cognitive event for those with pRBD was twice that of those without (HR= 2.04, 95% CI= 1.13; 3.69); models stratified by motor phenotypes yielded similar size, but less precise estimates (Figure 3-2), that were not formally statistically significant for the non-PIGD phenotype stratum.

Using the alternative definition, prevalence of pRBD increased from 21 to 25%, and results remained similar (Table S2-4). Finally, accounting for bias due to loss to follow-up using IPCW, effect estimates were also similar to the ones obtained without.

2.5 Discussion

In this large community-based Parkinson's disease study that followed new onset patients, RBD features in adult life were associated with faster cognitive decline, while there was only a trend observed towards a potentially faster motor symptoms progression among those with pRBD. Progression of motor dysfunction associated with pRBD was only faster among those who exhibited a PIGD motor subtype at baseline, while associations of pRBD and cognitive decline did not differ between subtypes. The average motor progression rate during follow-up in our cohort (1.9 points/year in UPDRS-III, Table S2-2) was similar to what has been reported (2.2 points/year) by a UK population-based study (Evans et al., 2011) of 132 patients with incident PD, followed for a similar average period (five years from PD diagnosis).

Prevalence of pRBD in our cohort is in the lower range of all estimates used in a recent meta-analysis (19 to 69%) (X. Zhang, Sun, Wang, Tang, & Xie, 2016) based on studies that recruited participants in select clinical settings rather than from communities. The higher prevalence of pRBD in our second (PEG2) compared to first patient enrolment wave (PEG1) might reflect the higher proportion of male participants enrolled in PEG2 (68% vs. 57%). Apart from being a chance finding, this may also reflect increased RBD awareness in more recent years, or other study participants' characteristics that differed at baseline.

Only one previous longitudinal population-based study (Gjerstad et al., 2008) has examined pRBD in PD, reporting on 231 Norwegian patients. Although that cohort had a much longer disease duration at baseline (on average 8.6 years for patients without pRBD and 11.1 for those with pRBD), compared with our population, its baseline prevalence of pRBD (15%) was equal to our first enrolment wave. Characteristics of participants with pRBD were also similar (i.e., more males, higher LED, longer PD duration, and similar frequency of dyskinesia). That study also found less tremor and lower overall UPDRS-III scores in participants with pRBD, but did not evaluate motor subtypes or UPDRS subscores, and it might also have been affected by selection for milder PD cases, due to the long average disease duration at baseline.

A faster progression of motor symptoms in PD with RBD has been noted previously in four smaller studies selecting participants from tertiary clinics (Bugalho & Viana-Baptista, 2013; Fereshtehnejad et al., 2015; Lavault et al., 2010; Ronald B Postuma, Bertrand, et al., 2012). In Canada, 36 PD patients underwent sleep laboratory evaluation (R B Postuma, Gagnon, Vendette, Charland, & Montplaisir, 2008); those with RBD had less tremor, but disease severity or other motor manifestations were not different over time. A longitudinal French study followed 100 PD patients from a University Hospital for two years (Lavault et al., 2010), and reported slightly higher UPDRS-III scores and on-medication axial subscores in pRBD affected patients at baseline and follow-up. In 61 newly diagnosed PD patients from a Neurology clinic in Portugal (Bugalho & Viana-Baptista, 2013) followed for two years, pRBD was associated with PIGD subtype at baseline, and with worse motor symptoms over time. In our study, pRBD was not associated with UPDRS-III scores or motor subtypes at baseline, but our cohort had a much shorter PD duration. Thus, while pRBD may not be an indicator of worse motor symptoms early

in the disease, among those with a PIGD subtype it may be a predictor of much faster motor decline, as suggested a decade ago (R B Postuma et al., 2008).

Another study evaluating rate of motor symptom progression in PD in relation to RBD, recruited 113 participants from two movement disorders clinics in Canada, and followed 76 for an average of 4.5 years, performing exams in sleep laboratories both times (Fereshtehnejad et al., 2015). Using cluster analysis, investigators identified three PD clinical subtypes; the one dominated by slowly progressing motor symptoms had the lowest prevalence of RBD (19%); another cluster featured a high (60%) pRBD prevalence and orthostatic hypotension at baseline, with intermediate motor progression. The third cluster exhibited the highest RBD prevalence (93%) combined with mild cognitive impairment in neuropsychiatric evaluations, orthostatic hypotension, axial motor subtype and the fastest motor progression. The clustering together of RBD features, faster motor progression, preponderance of axial (PIGD) subtypes, and/or cognitive progression, corroborate our findings. However, our results suggest that while presence of pRBD is associated with accelerated cognitive decline in all patients, its impact on motor progression seems to be restricted to PD with PIGD motor features.

In accordance with some other previous studies (Bugalho & Viana-Baptista, 2013; Fereshtehnejad et al., 2015; R B Postuma, Gagnon, Vendette, & Montplaisir, 2009), we found pRBD patients had generally worse non-motor symptoms at follow-up, with higher scores in UPDRS-I and in autonomic dysfunction symptoms items, especially higher frequencies of orthostatic hypotension symptoms and hallucinations. Implications of RBD for depressive symptoms in PD have not yet been investigated, but antidepressants may cause RBD-like

symptoms. In our cohort, GDS scores did not differ significantly between groups at both times, but the pRBD group reported more depression diagnoses and antidepressant medication use. When we adjusted models for these factors, however, estimates remained unchanged.

Our findings that pRBD accelerates time to reach MMSE≤ 24 corroborate those of several previous studies that found increased risk of dementia or cognitive decline with RBD (Nomura, Inoue, Kagimura, & Nakashima, 2013; Ronald B Postuma, Bertrand, et al., 2012; Romenets et al., 2012; Sinforiani et al., 2008). We report this finding for the first time in a cohort of PD patients sampled from an identifiable source population. In this cohort, we also obtained a similar annual rate difference (Table S2-2: Adjusted MD, with vs. without pRBD) of MMSE points decline as that reported from a multi-site international cohort of 423 PD patients (Chahine, Xie, et al., 2016), where pRBD patients declined on average 0.3 points in MOCA scores more per year than no-pRBD.

No experimental models of RBD in PD are available thus far (Fifel, Piggins, & Deboer, 2016), but the neurodegenerative nature of RBD is established. In RBD, the brainstem circuitry of the subcoeruleus nucleus and the ventromedial medulla, which promote normal motor activity suppression during REM sleep, are damaged (Fraigne et al., 2015; McKenna & Peever, 2017). While multiple neurotransmitter systems innervate these structures, cholinergic neurons play a central role. These are essential for maintenance of cognition, as is REM sleep in general, linking RBD with cognitive impairment and dementia. Additionally, damage to brainstem structures with diverse innervation, manifesting clinically as PIGD symptoms may link PIGD and RBD (since axial symptoms result mainly from non-dopaminergic impairment). In our cohort, pRBD

was not associated with motor subtype at baseline, but pRBD was an important marker for faster clinical motor progression in those with PIGD symptoms at baseline. Future studies expanding our understanding of this phenomenon are needed.

Using questionnaires to screen for RBD provides less specificity and sensitivity than objectively confirming a lack of atonia in polysomnography exams (Ronald B Postuma, Arnulf, et al., 2012). While questionnaires may introduce bias due to measurement error, they are the only feasible way to assess RBD in large populations. Longer 13-question screening questionnaires than ours, such as the RBD Screening Questionnaire (RBDSQ) and RBD-Hong Kong (RBD-HK) are available, but 94% sensitivity and 87% specificity were reached for a single question, that asks about 'acting out your dreams while asleep' (Ronald B Postuma, Arnulf, et al., 2012). Our pRBD definition aimed to increase specificity, but in sensitivity analyses with an alternative definition, results for motor and cognitive progression were similar. Furthermore, even unspecific motor behaviors or vocalizations during REM sleep have been found to be early indicators of PD (Sixel-Döring, Zimmermann, Wegener, Mollenhauer, & Trenkwalder, 2016).

Like most longitudinal studies, we lost patients during follow-up due to death or disabilities, but we used Cox models to account for censoring, in addition to IPCW to account for potential selection bias due to such censoring, resulting in estimates mostly unchanged. It is not clear whether the rate of progression of motor and cognitive symptoms in PD is indeed linear (Kuramoto et al., 2013) as assumed in most epidemiological studies of progression. Thus, to avoid this assumption, our main results are obtained from Cox models, which only assume that differences in hazard rates are multiplicative.

Ours is a large population-based study with movement disorder specialist confirmed PD diagnoses and motor assessments. We present evidence that pRBD features may be an early clinical marker of faster cognitive decline and progression of motor symptoms in PD, the latter particularly for patients with marked PIGD symptoms early in the disease. RBD-features may be a simple and useful screening for treatment trials and in clinical practice to identify those at risk for faster progression, who may benefit from pharmacological (changes in drug schemes) and non-pharmacological (including physical activity and prevention of falls) interventions.

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Co-authors 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 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.

2.7 Tables and Figures

Table 2-1. Baseline distribution of PD patients' characteristics: overall and by pRBD status.

Characteristics	Total[1]		With pRBD		Without pRBD		p-value: With vs. Without
	N or Mean	(% or SD)	N or Mean	(% or SD)	N or Mean	(% or SD)	
Study-related factors							
Total number	776	(100)	160	(21)	616	(79)	
Study wave, PEG1	310	(40)	45	(15)	265	(85)	0.001 [3]
PEG2	466	(60)	115	(25)	351	(75)	
Total with follow-up	477	(61)	90	(56)	387	(63)	
Average time, baseline to first follow-up, years[2]	3.4	(1.6)	3.4	(1.5)	3.4	(1.6)	
Min – Max	0.7 – 15.1		0.9 – 7.1		0.7 – 15.1		
Demographics							
Age at interview, years	70.5	(10.2)	70.0	(9.6)	70.6	(10.4)	0.50 [4]
Min – Max	34 - 92		37 - 92		34 - 92		
Sex, females	283	(37)	38	(23)	245	(40)	0.0001 [5]
Ethnicity, White	588	(76)	123	(76)	467	(76)	0.69 [5]
Latino	134	(17)	30	(19)	105	(17)	
Other	54	(7)	9	(6)	45	(7)	
Years of education	13.7	(4.5)	14.3	(3.7)	13.6	(4.7)	0.08 [4]
PD Clinical factors							
Age at PD diagnosis, years	67.4	(10.7)	66.4	(9.8)	67.7	(9.8)	0.04 [6]
Min – Max	23 - 89		35 - 88		23 - 89		
PD duration, years	3	(2.5)	3.5	(3.1)	3	(2.5)	0.04 [6]
Min - Max	0 - 16		0 - 16		0 - 15		
Motor subtype, Tremor Dominant	199	(26)	38	(24)	164	(27)	0.20 [7]
PIGD	471	(61)	97	(60)	376	(61)	
Indeterminate	106	(14)	27	(17)	79	(13)	
PD Treatment-related factors							
PD medication, any	692	(89)	151	(93)	544	(88)	0.12 [7]
LED, mg	404	(336)	459	(349)	388	(332)	0.06 [7]
Dyskinesia (n=424)	78	(19)	20	(19)	58	(18)	0.98 [7]
Medical factors (self-reported)							
High Blood Pressure	418	(54)	83	(51)	337	(54)	0.60 [7]
Diabetes, type 2	150	(19)	35	(22)	116	(19)	0.50 [7]
Cancer, any	213	(28)	40	(25)	175	(28)	0.50 [7]
Stroke	74	(10)	15	(9)	60	(10)	0.80 [7]

Heart attack	73	(9)	20	(12)	53	(9)	0.30 [7]
Traumatic Brain Injury	85	(11)	20	(12)	66	(11)	0.70 [7]
Anxiety	194	(25)	57	(35)	138	(22)	0.003 [7]
Depression	233	(30)	62	(38)	172	(28)	0.01 [7]
Anxiety medication use, any	141	(18)	37	(23)	104	(17)	0.03 [7]
Depression medication use, any	219	(28)	58	(36)	162	(26)	0.017
Lifestyle factors							
Smoker, never	429	(55)	84	(52)	346	(56)	0.60 [7]
Quit	320	(41)	73	(45)	249	(40)	
Current	26	(3)	5	(3)	22	(4)	
Smoking, pack-years	9	(19)	9.1	(17)	9.1	(17)	0.99 [6]
Physical activity levels, current							
Very low	493	(65)	108	(67)	388	(64)	0.20 [7]
Low	146	(19)	27	(17)	119	(20)	
Moderate	75	(10)	19	(12)	57	(9)	
High	48	(6)	7	(4)	41	(7)	
BMI (n=557)	27.5	(5.4)	27.6	(5.5)	27.6	(5.5)	0.82 [6]
underweight (<18.5)	174	(31)	37	(31)	137	(31)	0.50 [7]
normal (18.5-24)	17	(3)	3	(3)	14	(3)	
overweight (25-29)	205	(37)	44	(38)	161	(37)	
obese (>29)	161	(29)	32	(28)	129	(29)	
Average sleep duration current, hours	7.6	(1.8)	7.8	(1.9)	7.5	(1.8)	0.05 [6]
Lifetime coffee consumption							
Low	179	(26)	28	(19)	152	(28)	0.09 [7]
Medium	367	(53)	87	(59)	283	(51)	
High	150	(22)	33	(22)	117	(21)	
Alcohol use, never (n= 578)	66	(13)	7	(11)	59	(14)	0.30 [7]
Alcohol use, high lifetime consumption (n= 539)	279	(57)	58	(65)	223	(56)	0.40 [7]

[1]Total with RBD screening at baseline interview.

[2]Average follow-up time in years from baseline to first follow-up point. The total -average follow-up time for all 776 subjects, i.e. from baseline to last follow-up, was 4.8(1.6) (note: only the PEG 1 cohort had more than 1 follow-up exam).

[3]p-values obtained from **chi-square, testing equality of pRBD prevalence in PEG 1 vs. PEG 2.**

[4]p-values obtained from **t-tests, testing equality of characteristic comparing patients with vs. without pRBD.**

[5]p-values obtained from **chi-square, testing equality of characteristic comparing patients with vs. without pRBD.**

[6]p-value obtained from **linear regression of characteristic on pRBD status, adjusted** for sex and age at baseline interview.

[7]p-value obtained from **logistic regression of characteristic on pRBD status**, **adjusted** for sex and age at baseline interview. Ordinal logistic regression was used for characteristics with more than two categories (motor subtype, physical activity, BMI, coffee consumption).

Table 2-2. Baseline and follow-up motor and non-motor outcomes, by baseline pRBD status.

	With pRBD		Without pRBD		Adjusted p-value[2]
	N or Mean[1]	(% or 95% CI[1])	N or Mean[1]	(% or 95% CI[1])	
Baseline					
PD duration, years (SD)	3.5	(3.1)	3.0	(2.5)	
Motor (n=776)					
UPDRS-III, total	22.7	(19.8, 25.6)	23.1	(20.5, 25.7)	0.90
Tremor	2.8	(2.1, 3.4)	3.0	(2.4,3.6)	0.23
Rigidity	4.9	(4.2, 5.5)	4.9	(4.3, 5.5)	0.90
Bradykinesia	1.3	(1.0, 1.5)	1.2	(1.0, 1.4)	0.25
Axial	5.3	(4.4, 6.2)	5.2	(4.4, 6.1)	0.80
PIGD	1.1	(0.7, 1.5)	1.2	(0.8, 1.5)	0.96
HY≥ 3, yes	25	(16)	99	(16)	0.92
Non-motor (n=775)					
MMSE	26.9	(26.2, 27.6)	27.2	(26.6, 27.9)	0.04
GDS	3.4	(2.5, 4.2)	3.2	(2.4, 4.0)	0.57
First follow-up					
PD duration, years	6.3	(3.0)	6.1	(2.7)	
Motor (n=463)					
UPDRS-III, total	23.4	(18.6, 28.2)	22.6	(18.2, 27.0)	0.49
Tremor	2.3	(1.1, 3.4)	3.0	(2.0, 4.1)	0.03
Rigidity	5.2	(4.2, 6.3)	5.1	(4.1, 6.0)	0.53
Bradykinesia	1.6	(1.2, 2.0)	1.4	(1.1, 1.8)	0.04
Axial	5.7	(4.1, 7.3)	5.2	(3.8, 6.7)	0.19
PIGD	1.1	(0.4, 1.8)	1.1	(0.5, 1.8)	0.73
HY≥ 3, yes	22	(27)	94	(26)	0.50
Non-motor (n=477)					
MMSE	27.1	(26.0, 28.2)	27.7	(26.7, 28.7)	0.02
GDS	3.6	(2.3, 4.9)	3.3	(2.2, 4.5)	0.44
UPDRS-I[3]	9.3	(6.9, 11.7)	7.2	(5.0, 7.2)	0.005
UPDRS-II[4]	10.1	(6.9, 13.3)	8.6	(5.6, 11.5)	0.11
Autonomic symptoms score[5]	3.9	(2.6, 5.2)	3.2	(2.0, 4.4)	0.06
Orthostatic hypotension symptoms, yes[6]	53	(60)	213	(54)	0.24
Hallucinations, yes	21	(24)	43	(12)	0.001
UPDRS patient questionnaire	16.4	(11.9, 20.8)	14.1	(10.0, 18.2)	0.11

[1]Means and CI's adjusted for sex and PD duration at baseline or at first follow-up. Numbers and percentages (for HY, orthostatic hypotension symptoms and hallucinations) are crude.

[2]p-values obtained from linear (continuous) or logistic (binary) regressions of outcome on pRBD status, adjusted for: age at diagnosis, sex, PD duration at baseline or first follow-up, race, baseline wave (PEG1/2), and years of education for MMSE. For outcomes at first follow-up, baseline value was also included (except for UPDRS-I and II, because not available at baseline). Estimates and 95% CI's are shown in Table S2-3.

[3]UPDRS-I items: cognitive impairment, hallucinations, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome, sleep problems, daytime sleepiness, pain, urinary problems, constipation, lightheadedness, fatigue.
[4]UPDRS-II items: speech, saliva/drooling, chewing/swallowing, eating tasks, dressing, hygiene, handwriting, hobbies, turning in bed, tremor, getting off car/chair/bed, walking/balance, freezing.
[5]Autonomic symptoms items: urinary problems, constipation, lightheadedness, saliva/drooling, chewing/swallowing.
[6]Answer yes to item: lightheadedness.

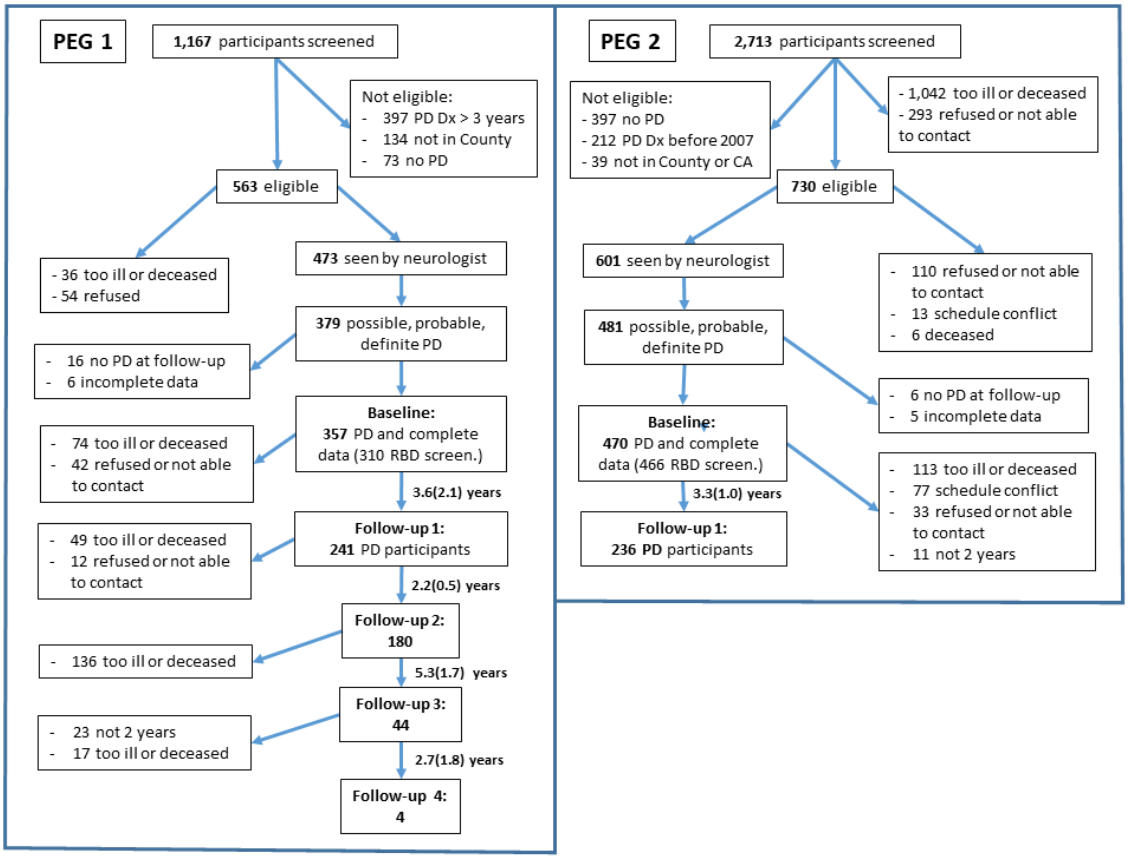


Figure 2-1. Flowchart of Parkinson's Environment and Genes (PEG) Study, first and second cohorts, baseline and follow-ups.

Progression events	Stratification	Total	N events (%) With pRBD[2]	Without pRBD[2]	HR[3] (95% CI)
UPDRS-III≥ 35	All (n=416)	115 (30)	26 (33)	89 (26)	1.48 (0.95, 2.32)
	PIGD phenotype (n=218)	83 (40)	19 (49)	64 (36)	1.92 (1.12, 3.27)
	other phenotypes (n=198)	32 (16)	7 (17)	25 (16)	1.25 (0.52, 3.00)
MMSE≤ 24	All (n=440)	63 (14)	16 (19)	48 (13)	2.04 (1.13, 3.69)
	PIGD phenotype (n=243)	39 (16)	9 (21)	30 (15)	2.17 (1.00, 4.71)
	other phenotypes (n=197)	24 (12)	7 (18)	18 (11)	2.11 (0.78, 5.72)

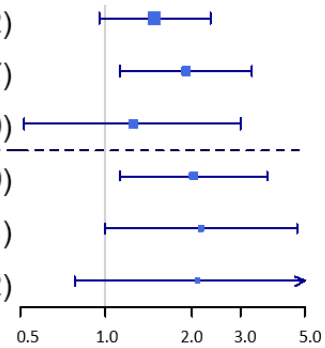


Figure 2-2. Hazard rate ratios (HR) estimated for clinical progression events and pRBD.

1- Total corresponds to those without the progression events at baseline.
2- Percentages refer to the total participants in each group (with and without pRBD).
3- Adjusted for age at diagnosis, sex, PD duration at baseline, race (minority yes/no), pack-years of smoking, baseline cohort (PEG1/2), and years of education for MMSE.

2.7 Supplementary material

Supplemental Methods

Description of creation of weights used in Inverse Probability of Censoring Weighting (IPCW)

According to the assumed causal structure depicted in the DAG shown in Figure S3-2, the goal of creating and applying weights, was to:

1) Make censoring independent of measured factors hypothesized of causing it (Z2= Age at diagnosis, PD duration, sex, race, PEG1 or 2, smoking, education) (here, we assume RBD also causes censoring):

If C=0: sw_c= Pr(C=0) / Pr(C=0|RBD=1,Z2)

If C=1: sw_c = [1-Pr(C=0)] / [1-Pr(C=0|RBD=1,Z2)]

2) Make RBD independent of (hypothesized) confounders (Z1: Age at diagnosis, PD duration, sex, race, PEG 1 or 2, smoking, education):

If RBD=1: sw_rbd = Pr(RBD=1) / Pr(RBD=1|Z1)

If RBD=0: sw_rbd = [1-Pr(RBD=1)] / [1-Pr(RBD=1|Z1)]

We fitted a marginal model (Cox model: exposure= RBD, outcome=time to progression event), weighted using one weight accounting for both censoring and confounding (sw = sw_rbd*sw_c).

Supplemental Results

Annual rate of progression

Results are shown in Supplemental Table 3-2. In adjusted linear regression models, we estimated the group with pRBD to increase on average 0.6 (95% CI -0.3,1.5) points more on UPDRS-III per year of follow-up, than those without pRBD, though the difference was not statistically significant. For UPDRS-III subscores, the progression rate for axial symptoms was the only significantly higher when comparing pRBD to no-pRBD patients. Finally, participants with pRBD had higher annual decline in MMSE scores, in adjusted models, the mean difference versus no-pRBD was -0.3 (95%CI -0.5, -0.1).

Table S2-1. Baseline distribution of PD patients' characteristics: overall and stratified by follow-up status.

Baseline characteristic	**Total[1]**		**With follow-up**		**Without follow-up**		**p-value[2]:** with vs. without follow-up
	N or Mean	% or SD	N or Mean	% or SD	N or Mean	% or SD	
Total[3]	827	(100)	477	(100)	350	(100)	
Study wave, PEG1	357	(43)	241	(68)	116	(32)	<.0001
PEG2	470	(57)	236	(50)	234	(50)	
pRBD, ever[4]	160	(21)	86	(19)	74	(24)	0.1
Demographics							
Age at baseline, years	70.8	(10.2)	69.0	(9.6)	73.1	(10.4)	<.0001
Sex, females	305	(37)	183	(39)	122	(34)	0.11
Race, White	633	(76)	361	(77)	271	(75)	0.73
Latino	139	(17)	76	(16)	63	(18)	
Other	1	(0)	30	(6)	27	(8)	
Years of education	13.6	(4.4)	14.1	(4.6)	13.1	(4.1)	0.00
PD related factors							
Age at PD diagnosis, years	67.7	(10.6)	66.2	(10.1)	69.7	(10.9)	<.0001
PD duration, years	3.0	(2.6)	2.8	(2.4)	3.3	(2.8)	0.00
Motor subtype PIGD	511	(62)	262	(56)	249	(69)	0.000
Tremor Dominant	205	(25)	131	(28)	74	(21)	
Indeterminate	111	(14)	75	(16)	36	(10)	
PD Treatment Related							
PD medication, any	738	(89)	418	(89)	319	(88)	0.59
LED, mg	399	(332)	377	(299)	428	(370)	0.02
Dyskinesia (only PEG2 n=424)	79	(19)	37	(18)	42	(19)	0.72
Medical Factors (Self-reported)							
High Blood Pressure	443	(53)	253	(54)	189	(52)	0.74
Diabetes, type 2	157	(19)	78	(17)	79	(22)	0.06
Cancer, any	226	(27)	129	(28)	96	(27)	0.74
Stroke	87	(11)	41	(9)	46	(13)	0.07

Heart attack	81	(10)	37	(8)	44	(12)	0.04
Traumatic Brain Injury	89	(11)	65	(14)	23	(6)	0.000
Anxiety	207	(25)	118	(25)	88	(24)	0.76
Depression	248	(30)	131	(28)	116	(32)	0.21
Anxiety medication use, any	150	(18)	82	(18)	68	(19)	0.64
Depression medication use, any	235	(28)	129	(28)	105	(29)	0.66
Lifestyle factors							
Smoker, never	452	(55)	265	(57)	187	(52)	0.08
Quit	346	(42)	190	(41)	155	(43)	
Current	31	(4)	12	(3)	19	(5)	
Smoking, pack-years	9.4	(19.5)	8.2	(17.6)	10.8	(21.4)	0.05
Physical activity levels, current	521	(64)	284	(62)	237	(68)	0.17
Very low							
Low	156	(19)	89	(19)	67	(19)	
Moderate	82	(10)	52	(11)	29	(8)	
High	54	(7)	36	(8)	18	(5)	
BMI	27.6	(5.5)	27.7	(5.2)	27.3	(5.9)	0.4
Average sleep duration, hours	7.6	(1.8)	7.3	(1.6)	7.9	(2.0)	<.0001
GDS score at baseline	3.7	(3.3)	3.1	(3.1)	4.5	(3.3)	<.0001
Lifetime coffee consumption	338	(45)	120	(28)	84	(26)	0.84
Low							
Medium	392	(52)	220	(51)	171	(53)	
High	154	(21)	88	(21)	66	(21)	
Alcohol use, ever	188	(84)	402	(87)	103	(87)	0.98
Alcohol use, high lifetime consumption	122	(66)	245	(58)	62	(53)	0.39

[1] Total enrolled at baseline, including 51 participants who did not complete RBD screening.

[2] p-values obtained from chi-square (for categorical measures) or from t-tests (for continuous measures), testing equality of baseline characteristic on with vs. without follow-up.

[3] N (Proportion) of total=827 (100%) with follow-up= 477 (56%) and without= 350 (44%).

[4] Percentage refers to total not missing data on RBD screening, n=776 (100%).

Table S2-2. Annual rate of progression (mean change in scores per year of follow-up), overall and by pRBD status.

	Mean change in score per year of follow-up (95% CI)						With vs. Without	
	Total		With pRBD		Without pRBD		Adjusted[1] MD (95% CI)	
UPDRS-III, total score (n=463)	1.9	(1.6, 2.2)	2.3	(1.6, 3.1)	1.8	(1.4, 2.2)	0.6	(-0.3, 1.4)
PIGD subtype only (n= 254)	1.9	(1.4, 2.4)	2.4	(1.3, 3.5)	1.8	(1.3, 2.3)	0.7	(-0.5, 1.9)
Other phenotypes (n=209)	1.8	(1.4, 2.2)	2.1	(0.9, 3.4)	1.7	(1.1, 2.2)	0.4	(-0.6, 1.5)
UPDRS-III sub-scores,								
Tremor	0.1	(0, 0.2)	0.1	(-0.1, 0.3)	0.1	(0, 0.2)	0.1	(-0.1, 0.2)
Rigidity	0.3	(0.2, 0.4)	0.4	(0.2, 0.6)	0.3	(0.2, 0.4)	0.1	(-0.1, 0.3)
Bradykinesia	0.2	(0.1, 0.2)	0.2	(0.1, 0.2)	0.1	(0.1, 0.2)	0.0	(-0.1, 0.1)
Axial	0.7	(0.6, 0.9)	0.9	(0.7, 1.1)	0.7	(0.6, 0.8)	0.2	(0, 0.5)
PIGD	0.2	(0.2, 0.3)	0.3	(0.1, 0.4)	0.2	(0.2, 0.3)	0.0	(-0.1, 0.2)
MMSE (n=477)	-0.3	(-0.3, -0.2)	-0.5	(-0.6, -0.3)	-0.2	(-0.3, -0.1)	-0.2	(-0.4, -0.1)
PIGD subtype only (n= 268)	-0.3	(-0.4, -0.2)	-0.7	(-1.0, -0.4)	-0.2	(-0.3, -0.1)	-0.4	(-0.7 -0.1)
Other phenotypes (n=209)	-0.2	(-0.3, -0.1)	-0.2	(-0.4, 0.1)	-0.2	(-0.2, -0.1)	0.0	(-0.3, 0.2)
GDS	0.2	(0.1, 0.3)	0.2	(0, 0.4)	0.2	(0.1, 0.3)	0.0	(-0.2, 0.2)

[1]Mean differences obtained from linear regression of rate measure on pRBD status, adjusted for age at diagnosis, sex, race (binary), PD duration at baseline, smoking in pack-years, baseline wave, and years of education for MMSE.

Table S2-3: Motor and non-motor outcomes scores, overall and differences by baseline pRBD status.

	Total[1]		With vs. without pRBD	
	Mean	**(95% CI)**	**Adjusted MD[2]**	**(95% CI)**
Baseline				
Motor (n= 776)				
UPDRS-III, total	21.59	(20.82,22.36)	-0.16	(-2.07,1.75)
UPDRS-III, Tremor	3.14	(2.97,3.32)	-0.28	(-0.73,0.17)
UPDRS-III, Rigidity	3.49	(3.32,3.66)	0.03	(-0.39,0.45)
UPDRS-III, Bradykinesia	1.14	(1.08,1.2)	0.08	(-0.06,0.23)
UPDRS-III, Axial	4.62	(4.38,4.86)	0.08	(-0.49,0.65)
UPDRS-III, PIGD	1.66	(1.55,1.77)	-0.01	(-0.28,0.25)
Non-motor (n=775)				
MMSE	27.50	(27.31,27.69)	-0.44	(-0.87,-0.02)
GDS	3.71	(3.48,3.93)	0.17	(-0.4,0.73)
First follow-up				
Motor (n=463)				
UPDRS-III, total	25.25	(24.1,26.4)	1.01	(-1.83,3.84)
UPDRS-III, Tremor	0.14	(3.17,3.71)	-0.76	(-1.44,-0.08)
UPDRS-III, Rigidity	3.94	(3.68,4.21)	0.21	(-0.44,0.85)
UPDRS-III, Bradykinesia	1.51	(1.43,1.6)	0.23	(0.01,0.44)
UPDRS-III, Axial	5.96	(5.58,6.33)	0.59	(-0.29,1.47)
UPDRS-III, PIGD	1.94	(1.77,2.11)	0.07	(-0.33,0.48)
Non-motor (n=477)				
MMSE	27.65	(27.39,27.9)	-0.70	(-1.27,-0.12)
GDS	3.87	(3.57,4.16)	0.30	(-0.47,1.07)
UPDRS-I[3]	12.42	(11.85,12.99)	2.06	(0.61,3.52)
UPDRS-II[4]	14.99	(14.19,15.79)	1.56	(-0.36,3.48)
Autonomic symptoms (score)[5]	5.29	(4.98,5.59)	0.74	(-0.04, 1.52)
UPDRS patient questionnaire[6]	24.65	(23.54,25.76)	2.25	(-0.44, 4.94)

[1] Crude means

[2] MD=Mean Difference. Covariates included in linear regression models: age at diagnosis, sex, PD duration at baseline or follow-up, race, baseline wave, and years of education for MMSE.

[3]UPDRS-I items: cognitive impairment, hallucinations, depressed mood, anxious mood, apathy, feaures of dopamine dysregulation syndrome, sleep problems, daytime sleepiness, pain, urinary problems, constipation, light headedness, fatigue.

[4]UPDRS-II items: speech, saliva/drooling, chewing/swallowing, eating tasks, dressing, hygiene, handwriting, hobbies, turning in bed, tremor, getting off car/chair/bed, walking/balance, freezing.

[5] Score from UPDRS IB item: Light headedness.

[6] Score from UPDRS IA item: Hallucinations.

Table S2-4. Hazard rate ratio estimates for motor and cognitive progression events comparing with pRBD to without pRBD[1]: sensitivity analyses.

Progression events	Stratification	Main Results: Figure 2		Main Results: IPCW[2]		pRBD alternative definition		pRBD alternative: IPCW	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
UPDRS-III ≥ 35	All (n=416)[3]	1.48	(0.95, 2.32)	1.41	(0.92, 2.15)	1.53	(1.01, 2.31)	1.48	(1.00, 2.20)
	PIGD phenotype (n=218)	1.92	(1.12, 3.27)	1.77	(1.14, 2.75)	1.53	(0.94, 2.48)	1.55	(1.00, 2.40)
	other phenotypes (n=198)	1.25	(0.52, 3.00)	0.90	(0.36, 2.27)	1.64	(0.69, 3.91)	1.18	(0.51, 2.74)
MMSE ≤ 24	All (n=440)[3]	2.04	(1.13, 3.69)	1.51	(0.83, 2.76)	1.94	(1.13, 3.43)	1.79	(1.01, 3.16)
	PIGD phenotype (n=243)	2.17	(1.00, 4.71)	1.75	(0.79, 3.90)	1.57	(0.78, 3.16)	1.90	(0.91, 3.97)
	other phenotypes (n=197)	2.11	(0.78, 5.72)	1.31	(0.55, 3.13)	2.74	(1.03, 7.25)	1.58	(0.69, 3.60)

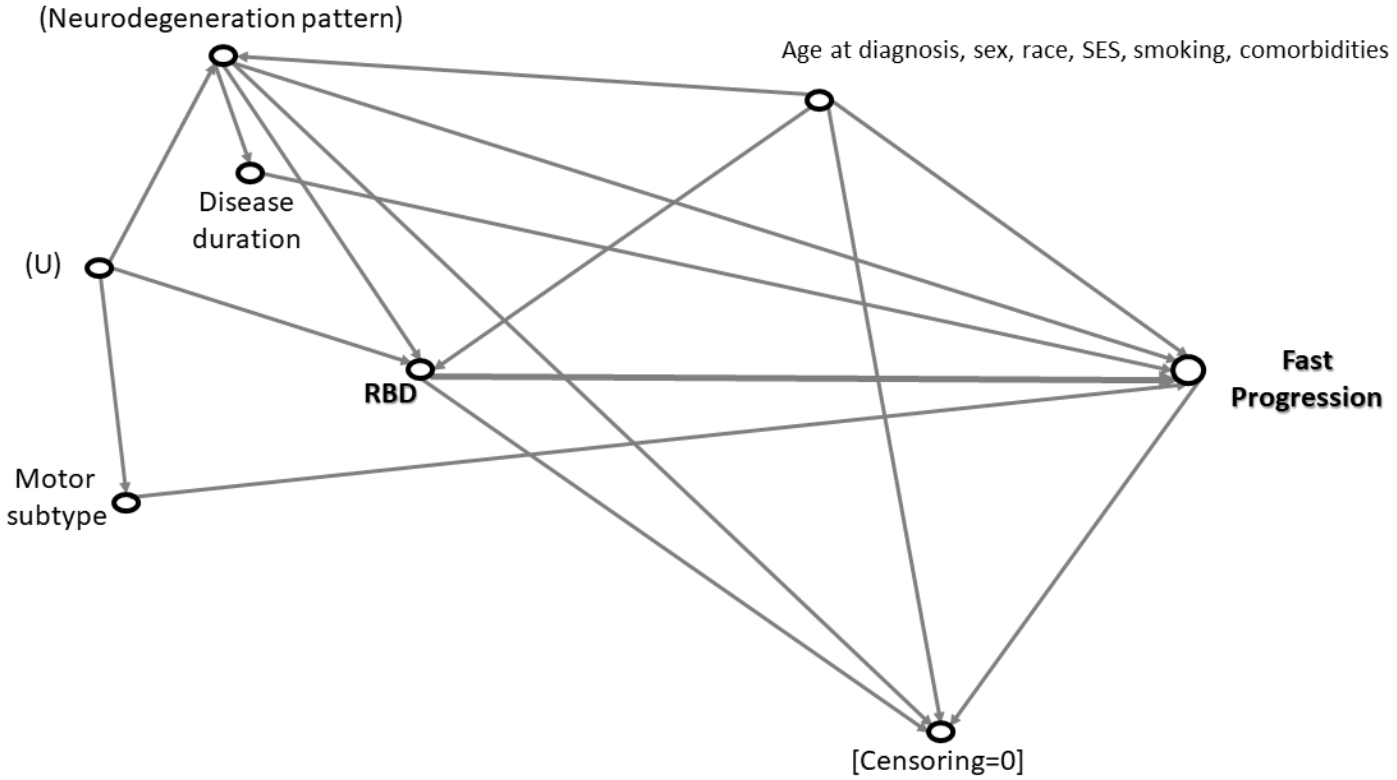
[1] All models are adjusted for: age at diagnosis, sex, PD duration at baseline, race (minority yes/no), pack-years of smoking, baseline wave (PEG1/2), and years of education for MMSE.

[2] IPCW= Inverse Probability of Censoring Weighting. Procedures to obtain weights are described in Supplemental Methods.

[3] Total corresponds to those without the respective event (UPDRS-III ≥ 35 or MMSE ≤ 24) at baseline.

Thinking about your sleep as an adult (age >18), do you know (or has anyone ever told you) that your sleep at night was characterized by:				
	This definitely happened	This may have happened but I cannot be sure	It's unlikely that this has happened	I don't know whether this has happened
Acting out in your dreams?	1	2	3	4
Talking, yelling, or screaming in your sleep?	1	2	3	4
Walking in your sleep?	1	2	3	4
Aggressive behaviors (hitting, punching) in your sleep?	1	2	3	4

Figure S2-1. Screening questionnaire used to measure features of RBD in adult life.



Supplemental Figure 2-2. Proposed Directed Acyclic Graph depicting hypothesized relation of factors considered in analyzes. Variable in parenthesis are not measured, and in brackets represent analysis conditioned on. RBD=REM Sleep behavior disorder. U=unknown background factors. SES- socioeconomic status.

3 Parkinson's Disease-Related Risk Factors for Insomnia and Excessive Daytime Sleepiness in a Population-based Study

3.1 Abstract

Introduction: Insomnia and excessive daytime sleepiness are the most common sleep disturbances in Parkinson's disease. We aimed at estimating contributions of severity of PD motor and non-motor features and dopaminergic treatments to prevalent insomnia and EDS in patients who on average are within six years of an initial PD diagnosis. In addition, we explored contributions of PD features to changes in insomnia and EDS symptoms within a two-year period.

Methods: In a population-based cohort of PD, we estimated cross-sectional and longitudinal associations of PD-related risk factors with sleep scores of insomnia and EDS, using linear regression models and linear mixed models adjusted at minimum for age, gender and PD duration.

Results: Information was available for a total of 477 patients, at an average PD duration of 6.3 years, and for 156 sleep information was also available for one additional follow-up on average 2.2 years later. In cross-sectional models, PIGD motor signs, worse autonomic symptoms, and complex non-motor symptoms (depression, anxiety, apathy, hallucinations and dopamine dysregulation syndrome) were associated with both EDS and insomnia, Motor UPDRS, tremor sub-scores and motor complications were associated only with insomnia, but levodopa dose was associated strongly with EDS than insomnia. In longitudinal models, only those with lower motor or autonomic symptom scores at the first follow-up showed further increase in insomnia

scores after two additional years, suggesting there may be a saturation effect of how these features affect further worsening of insomnia symptoms over PD course.

Discussion: Although causes of sleep problems of are multifactorial in PD, we estimated the contribution of some PD-related features to insomnia and EDS symptoms, showing that PD features are associated with different impacts in sleep, and providing insight into how sleep symptoms change over time.

3.2 Introduction

Sleep problems have been identified as important symptoms in Parkinson's disease (PD) since the first description of the PD syndrome by Dr. James Parkinson in 1817 (Parkinson, 2002). The most frequent sleep or sleep-related problems patients report are excessive daytime sleepiness (EDS), insomnia (Suzuki, Miyamoto, Miyamoto, & Hirata, 2015) and REM sleep behavior disorder (RBD). Insomnia and EDS are sleep-wake disturbances that may indicate disruption of the circadian rhythm, which is considered an important co-occurrence as part of the neurodegenerative process characteristic of PD (Fifel, 2017; Li, Wang, Wang, Hu, & Liu, 2016).

Insomnia is the difficulty to initiate or maintain sleep and, when it manifests chronically, insomnia has well-known negative consequences for health status and health-related quality of life (Avidan et al., 2013). It is a common health problem in the general population with a higher prevalence in older individuals, women, and those suffering from depression and anxiety (Hays, Martin, Sesti, & Spritzer, 2005). PD patients usually do not have trouble initiating sleep, thus insomnia manifests mainly as a difficulty to maintain sleep, resulting in sleep fragmentation and early awakening (Stefani & Högl, 2019).

Excessive daytime sleepiness (EDS), also referred to as daytime somnolence, hypersomnia, hypersomnolence, and excessive sleepiness, is a subjective complaint characterized by a difficulty in remaining awake, usually accompanied by sleep initiation if the person stays inactive (Daroff, 1991). This is especially harmful in instances when individuals fall asleep while driving, and it is a predictor of worse health outcomes, such as cognitive impairment, as previously reported for aging individuals in the United States (Tsapanou et al., 2015). EDS has been found to be more common in PD patients than in the general population (Marinus, Visser, Van Hilten, Lammers, & Stiggelbout, 2003), and can be attributable to primary central disorders of hypersomnolence, as defined in the International Classification of Sleep Disorders (ICSD) (ICSD-3, 2014; Sateia, 2014). These disorders can result from insomnia or bad sleep quality, circadian rhythm abnormalities, or of other related clinical factors, such as pharmacotherapy for anxiety, and depression, which are common in PD (Sateia, 2014).

In the last decade, a number of studies aimed to identify risk factors for insomnia and/or EDS sleep disorders in PD (Amara et al., 2017; Gjerstad, Wentzel-Larsen, Aarsland, & Larsen, 2007; Junho, Kummer, Cardoso, Teixeira, & Rocha, 2018; Porter, MacFarlane, & Walker, 2008; Ratti et al., 2015; Tandberg, Larsen, & Karlsen, 1999; Tholfsen, Larsen, Schulz, Tysnes, & Gjerstad, 2015; Xiang et al., 2019; K. Zhu, van Hilten, & Marinus, 2016b, 2016a) and reported associations with longer PD duration, worse motor disability, dopaminergic medications, depression and anxiety, and worse autonomic symptoms. However, which PD-related clinical factors are indeed associated with these sleep disorders needs to be further elucidated since previous studies reported inconsistent results, likely because studies relied mainly on small and

strongly selected patient samples from tertiary clinics, and employed statistical models that aimed at generating prediction models rather than identifying causative associations, for which possible confounding factors need to be carefully considered.

Better insight into what causes sleep problems in PD will encourage approaches that aim to improve clinical care and quality of life of patients. To achieve this, it might be more informative to elucidate the role of sleep problems in PD with modern and valid methods in a population-based study. Previously, we investigated the role of REM sleep behavior disorder on PD progression. Relying on the same population-based cohort of PD, we are now estimating the contributions of severity of PD motor and non-motor features and dopaminergic treatments to prevalent insomnia and EDS in patients who on average are within six years of an initial PD diagnosis. In addition, we are exploring the contributions of the same PD features to changes in insomnia and EDS symptoms within a two-year period.

3.3 Methods

Research Ethics

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.

Study design

The Parkinson's Environment and Genes Study (PEG), identified new-onset (up to 5 years after diagnosis) PD cases as two independent cohorts assessed at baseline from 2001 to 2007 (PEG 1),

and from 2011 to 2017 (PEG 2), from the entire population of three California counties (Wang et al., 2011). 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 for a second follow-up visit, on average 2.2 (±0.5) years after the first follow-up. At all time points, participants were examined at a clinic in their county of residence by movement disorders specialists affiliated with the PEG study, who confirmed the diagnosis of Probable or Definite idiopathic PD according to common criteria (Wang et al., 2011), and evaluated motor signs and symptoms, preferably off PD medications. Patients who were classified as Possible PD were scheduled a re-see appointment approximately after one year of the initial assessment, but they were not excluded from the study sample until a No PD diagnosis was confirmed.

Data collected

Study neurologists examined patients and scored motor disability using the Unified Parkinson's Disease Rating Scale (UPDRS and later MDS-UPDRS was adopted, parts IA, III and IV) and Hoehn and Yahr staging (HY). During all study visits, trained research assistants interviewed participants to collect demographic, lifestyle, and medical history information, including current PD medication use and dosage. Additional standardized instruments were adopted only during follow-up visits, including some to measure insomnia and EDS, as well as the UPDRS Patient Questionnaire (parts IB and II), which assesses non-motor and motor impact of PD on experiences of daily living (items include: sleep problems, daytime sleepiness, pain, urinary problems, constipation problems, light headedness, fatigue, speech, saliva and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting, doing hobbies, turning in bed, tremor, getting out bed/car/chair, walking/balance, and freezing).

We relied on the Sleep Survey of the Medical Outcomes Study (MOS-Sleep) as our main assessment tool for symptoms of insomnia and EDS. This instrument 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 initiation, maintenance, quantity/duration, and perceived adequacy of sleep, as well as respiratory problems and somnolence. This instrument's content is comparable to two questionnaires widely used in sleep and PD research, the Pittsburgh Sleep Quality Index (PSQI) and the Parkinson's Disease Sleep Scale (PDSS) (Chaudhuri et al., 2002). The PSQI also inquires about symptoms in the past four weeks, while the PDSS asks patients to recall items only over the past week, but includes three additional items focused on motor dysfunction (such as presence of tremor at awakening).

The MOS-Sleep has been validated in and used to study populations with chronic diseases other than PD. Its items are summarized to create five sleep scores (sleep disturbance, somnolence, sleep adequacy, snoring, and shortness of breath during sleep) and two sleep problems indices (I and II). Each of these range from 0 to 100, with higher scores indicating worse sleep quality, except for the adequacy score, which has a reverse rating with higher scores indicating better sleep quality.

For our main outcomes of interest, we generated 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, and

for somnolence (items: drowsy during day, have trouble staying awake during the day, take naps), as a measure of EDS.

PD medication information, including levodopa and dopamine agonist use, were summarized as described previously into a levodopa equivalent dose (Tomlinson et al., 2010). PD motor subtypes of Postural Imbalance and Gait Deficiency (PIGD), Tremor Dominant (TD), or indeterminate were also calculated as ratios of specific UPDRS-III sub-scores, as described previously (Keener et al., 2018). Additionally, UPDRS-III sub-scores were calculated by summing specific items corresponding to tremor, rigidity, bradykinesia (body bradykinesia), axial (speech, neck rigidity, arise from chair, posture, postural stability, and gait) and PIGD (Gait and Postural Instability). UPDRS-III scores were corrected for items missing due to impossibility of evaluation (such as Arise from Chair when the patient is paraplegic), and also when only an exam while 'on' PD medication was possible, as previously described (Ritz, Rhodes, Bordelon, & Bronstein, 2012).

Statistical analysis

We conducted analyses in statistical software package SAS (SAS 9.4, SAS Institute, Cary, NC) version 9.4, and figures were generated in R. Insomnia and EDS scores were normally distributed in univariate and across multivariable analyses including risk factors of interest, and sex, age and PD duration at the time the sleep quality measures were collected.

To be able to compare estimates of how PD-related factors affect insomnia and EDS scores, we chose to standardize the sleep scores centering on the mean of zero and a standard deviation of

one. To visualize how PD-related factors (PD duration, age at diagnosis, UPDRS-III, UPDRS-IA, and levodopa equivalent daily dose) may influence sleep symptoms, we first plotted crude standardized insomnia and EDS scores according to these factors, stratifying by gender and obtaining Pearson correlation coefficients. For each risk factor of interest, we also estimated mean differences in standardized MOS-Sleep scores, modeling score increases for continuous risk factors in (maximum likelihood) linear regression models (implemented with Proc Genmod; SAS 9.4) including potential confounders; i.e., as a minimum set we included sex, age at interview, and PD duration. We also plotted residuals versus predicted values to assess whether the linear regression assumptions were satisfied. In sensitivity analyses, additional potential confounders were included in the models, guided by mechanisms we proposed and depicted in Directed Acyclic Graphs (Supplemental figure 1, and detailed in the Results section).

We used linear mixed models (implemented with Proc Mixed in SAS 9.4), to examine between-subject and within-subject (over time) associations with change in standardized insomnia and EDS scores for the following risk factors: PD duration, UPDRS-III, levodopa dose, UPDRS-IA, and autonomic symptoms measured at the first time sleep data was collected. These models assess the influence of these factors on change in sleep measures through interaction terms between the risk-factors and follow-up time, and they are adjusted for sex and time-varying age and PD duration, in addition to UPDRS-III (in the models for levodopa) and levodopa dose (in the models for UPDRS-IA and autonomic symptoms). The regression coefficient (β) for the main effect in these models represents the average population mean difference in sleep measure scores at the first time point, for example, when assessing the influence of a UPDRS-III$\geq$ 35 vs. < 35. We also included random effect terms for the intercept and slope in these models, based on plots

of individual trajectories over time, and applied a compound symmetry covariance pattern for the correlated observations over time (assuming that variance is constant across time points, i.e. correlations between any pair of measurements are the same, regardless of the time interval). Because only two time points were available, we only included a linear term for the follow-up time variable in these repeated measures models.

Risk factors were dichotomized for use in the mixed repeated measures models. PD duration at its median of 6.5 years at first sleep assessment, UPDRS-III at 35 points; LED at 500 mg for comparability since it has been the median reported previously in studies (Ratti et al., 2015; Tandberg et al., 1999; K. Zhu et al., 2016a); UPDRS-IA, at 5 points and the autonomic symptoms score, at 8 points, corresponding to the respective 75^{th} percentile of the distribution for these scores in our study).

3.4 Results

Our study included 477 PD patients who completed the MOS-Sleep at least once; a majority was male (62%), white (77%), and assessed for sleep quality on average 6.3 ± 3.0 years after their first PD diagnosis at which time 69% exhibited a PIGD motor phenotype (Table 3-1). From among sleep domains we assessed with MOS scores, EDS received the highest absolute score (mean 42.4 ± 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) (Figure S3-2). The average UPDRS-III score was 25.2 ± 12.5, with 102 (23%) patients having a score of 35+ points, and 110 (26%) having reached a Hoehn and Yahr stage (HY) of 3+ (Table 3-1).

Patients diagnosed at younger ages and with longer PD duration had worse insomnia symptom scores. Age at PD diagnosis and disease duration were not correlated with EDS (Figure 3-1). UPDRS-III, LED, autonomic symptoms and UPDRS-IA all were positively correlated with both sleep scores. We observed no differences between men and women.

Cross-sectional multivariate linear regressions analyses adjusted for sex, age at time of measurement, and PD duration show that for each 5-point increase in the UPDRS-III score we estimated an average increase of 0.10 standard deviations (95% CI: 0.02, 0.17) in the insomnia score, and of 0.04 SD in EDS scores (95% CI: 0.002, 0.08) (Table 3-2). Tremor-related motor signs increased insomnia scores, with a mean difference of 0.16 (95% CI: 0.01, 0.31) (Table 3-2), but not EDS. Bradykinesia increased EDS scores (mean difference of 0.59; 95% CI: 0.04, 0.97) whether or not we adjusted for levodopa dose, but the association was greatly reduced after adjustment for the geriatric depression scale (GDS) score (0.25; 95% CI: -0.21, 0.71, data not shown). PIGD-related motor features were associated with both higher insomnia and EDS scores, as shown in Table 3-2.

A one-point difference in UPDRS-IV scores (motor complications such as dyskinesia), was associated with 0.05 (95% CI: 0.02, 0.09) SD difference in insomnia scores (Table 3-2), but not with EDS and did not depend on levodopa use, i.e. restricting to levodopa only users, or adjusting for levodopa dose and/or for UPDRS motor scores (results not shown).

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 3-1). Levodopa dose was associated with insomnia and EDS scores, but only for EDS did the estimate differ statistically significantly from zero (mean difference of 0.04; 95% CI: 0.01, 0.08 for every 100 mg increase (Table 3-2), and the strongest associations were observed among PIGD participants (0.06; 95% CI: 0.03, 0.09).

Severity of non-motor symptoms measured by the UPDRS-IA score (cognitive impairment, hallucinations, depression and anxiety, apathy, and features of dopamine dysregulation syndrome), and also autonomic nervous system symptoms (constipation, urinary problems, light headedness, saliva/drooling, chewing/swallowing) were strongly associated with insomnia and EDS cross-sectionally (Table 3-2), even when adjusting for motor UPDRS.

Longitudinal information on insomnia and EDS scores was available for 156 participants from the PEG 1 cohort at second follow-up. Average EDS scores increased over time (crude mean score increase in EDS scores within-person of 3.0 points (95% CI: -0.7, 6.6) after 2.2 ± 0.5 years of average follow-up). Whereas insomnia average scores did not change, the crude difference was -1.4, 95% CI: -4.6, 1.8.

In adjusted linear mixed models, estimates obtained for cross-sectional differences in EDS and insomnia scores according to the PD features evaluated were similar to the ones described in Table 3-2. Insomnia scores improved during follow-up for those with higher UPDRS-III, LED for levodopa, and autonomic symptom scores (compared to those with lower PD severity measured by such factors) at first assessment time, shown in estimated for interaction terms with follow-up time in Table 3-3. None of the PD features we evaluated were related to changes in

EDS scores over the 2 years of follow-up. LED for dopamine agonists only was not associated with sleep problems at either time point or over time (results not shown).

Participants without follow-up information (N=321) on sleep were of similar age and sex, but had longer average PD duration (7 vs. 5 years), and higher UPDRS motor and non-motor scores (Table S3-1). However, EDS and insomnias average scores at first follow-up were similar among those who lost to follow-up or not.

3.5 Discussion

In this large population-based study of Parkinson's disease, we assessed the contributions of PD-related features to the prevalence of insomnia and EDS symptoms among patients with on average six years of disease duration; for a subgroup of 156 patients we also had information from an additional follow-up two years later. We found that longer PD duration, higher LED, UPDRS-IA and autonomic symptom score were positively associated with EDS and insomnia, cross-sectionally. On the other hand, motor symptoms, particularly tremor and motor fluctuations, measured by UPDRS-III and IV, were related to increased insomnia but not EDS scores. We also found that only patients with lower motor or autonomic symptom score at the first follow-up showed further increase in insomnia scores after two additional years, suggesting a saturation effect.

Motor scores were associated with both higher insomnia and EDS scores, but affected insomnia more strongly. Specifically, tremor sub-scores and motor fluctuations were strongly associated with insomnia symptoms. Insomnia may accompany PD motor disability due to worsening

circadian disruption resulting from neurodegeneration of sleep-wake regulatory centers in PD (Mantovani et al., 2018), and motor symptoms may also directly disrupt sleep and result in insomnia. Tremor during "off" states at night may lead to increased sleep fragmentation, resulting from reemergence of resting tremor during micro-arousals, body movements and sleep-state changes (mainly from NREM to REM) (French et al 2016), or motor activity from tremor or motor fluctuations may disrupt the circadian system directly (Fifel, 2017).

Thus far, three larger studies relating motor disability to insomnia have mostly been descriptive but generally corroborate our findings that motor symptoms and complications are associated with insomnia. A large population-based French study (COPARK), reported cross-sectional results for 636 PD patients who responded to the PSQI questionnaire (Ratti et al., 2015) with PD duration similar to our study's (mean of 6.3 years); they also found higher motor UPDRS scores in those with sleep disturbance (defined as PSQI score above 5, similar in content to our insomnia measure) but did not adjust for age, sex, or PD duration. A population-based Norwegian cohort (n=231) also reported insomnia to be associated with higher motor UPDRS scores, but these estimates were not statistically significant and, again, not adjusted for age, sex or other potential confounders (Gjerstad et al., 2007). In addition, this population had a higher PD duration at time of study (average of 9.8 years with insomnia and 7.8 without insomnia). A hospital-based longitudinal Dutch study (PROPARK) assessed sleep quality in 412 patients (average PD duration of 10.6 years) with 27% reporting insomnia, and these patients also exhibited more motor disabilities including motor complications and fluctuations cross-sectionally (K. Zhu et al., 2016b).

Motor scores, on the other hand, were only weakly associated with EDS cross-sectionally, and associations were mainly seen for bradykinesia. Only one other study in a clinical population from China has reported specifically on the association of bradykinesia scores and EDS (Xiang et al., 2019). Despite a slightly shorter average PD duration (5.1 years), these Chinese patients scored higher on the motor UPDRS scale, and patients were recruited from specialized clinics only. Similar to our results, an international multicenter study of 423 PD patients (PD duration mean of 6.7 years) saw no association between motor UPDRS scores at baseline, or at two additional annual follow-up exams with EDS (Amara et al., 2017; Simuni et al., 2015), but they did not report results on UPDRS motor sub-scores assessing bradykinesia.

As suggested previously by others (A. Höglund, Broman, Pålhagen, Fredrikson, & Hagell, 2015), EDS does not seem to be related to PD motor dysfunction resulting from primary nigrostriatal dopaminergic degeneration, but rather to features like autonomous nervous system dysfunction, suggesting the degeneration of other neurotransmitter systems. For example, EDS has been related to the degeneration of the alertness system, including hypocretin neurons in the hypothalamus, noradrenergic in the Locus Coeruleus, and serotonergic in the Dorsal Raphe Nuclei in some post-mortem studies, as well as in studies of brain imaging in clinical samples (Wilson, Giordano, Turkheimer, Chaudhuri, & Politis, 2018), which would explain in part the associations we saw with bradykinesia and depressed mood.

Unlike previous clinical-based studies, most of our PD patients were classified as PIGD, and, as expected, 55% of those classified as tremor dominant at baseline assumed a PIGD phenotype during follow-up. PIGD motor sub-scores (from UPDRS motor) were strongly positively

associated with both insomnia and EDS in cross-sectional analyses (Table 3-2). Additionally, axial signs were associated with worse EDS. PIGD and axial symptoms as well as non-motor symptoms are less responsive to levodopa treatment than other motor manifestations (Ratti et al., 2015), and they are treated with higher dosages. It has been proposed that treatment with levodopa may affect circadian rhythms directly in PD patients through mechanisms that uncouple circadian and sleep regulation (Mantovani et al., 2018), such as altering melatonin secretion and action. In our study, levodopa dose was associated with higher symptom scores for EDS and insomnia, and this was even stronger in those with a PIGD phenotype.

Results regarding the contribution of levodopa and dopamine agonists therapy and sleep problems have been conflicting, but, in general, dopaminergic treatment has been associated with worse EDS. Two previous studies, one population-based from Norway, and the hospital-based Dutch study (Tandberg et al., 1999; Tholfsen et al., 2015; K. Zhu et al., 2016a), like us, found slightly higher levodopa dosage in PD with EDS cross-sectionally, and did not find not LED to predict worse LED over time. However, the Norwegian ParkWest population-based study (Tholfsen et al., 2015) reported no association of LED and EDS after on average five years from PD diagnosis. In this cohort, a higher proportion of patients used dopamine agonists, 57% compared to 38% in PEG. The ParkWest regression models for EDS adjusted for age, gender, PD duration, but also PIGD phenotype, insomnia, UPDRS motor, ADL, MMSE and depression scores. We only adjusted for gender, age, PD duration, and UPDRS motor scores.

As previously reported (Amara et al., 2017; Tholfsen et al., 2015; K. Zhu et al., 2016b), we also found autonomic symptoms and other non-motor manifestations, mainly measured by UPDRS-

IA score (called complex symptoms), to be associated with worse EDS and insomnia. Some non-motor symptoms of PD can directly induce sleep fragmentation, such as nocturia; in fact, we see a strong association between a measure of urinary problems and sleep symptoms. Some non-motor manifestations are associated with circadian rhythms disruption and we observed associations also between autonomic symptoms (light headedness, constipation, saliva and drooling, chewing and swallowing, urinary symptoms) scores and sleep problems, in both our cross-sectional and longitudinal models.

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 such as blood pressure, urinary, and gastrointestinal. Degeneration of circadian system structures, that induce circadian disruption would thus be manifesting in peripheral organs as autonomic dysfunction, and also induce changes in sleep structure and quality.

While PD severity predicted worse sleep cross-sectionally, longitudinal analyses suggested that better of PD patients (according to UPDRS-III, LED and autonomic symptoms), progressed to worse insomnia over time. This may indicate that PD motor and non-motor features reach a ceiling after which insomnia does not worsen anymore; in fact this has previously been reported for both EDS and insomnia in smaller studies (Gjerstad et al., 2007; Arja Höglund et al., 2019).

About 40% of participants were lost to follow-up after our cohort baseline and, therefore, we had no information about EDS and insomnia symptoms for these patients. They were older and had longer PD duration at cohort baseline, and also reported slightly higher sleep duration average at baseline (7.9 compared to 7.3, t-test p-value <0.0001). If this difference in sleep duration reflects sleep problems such as insomnia and EDS, this could have impacted our estimates. For example, if participants lost, who had longer PD duration, also had more EDS, our estimates for association of PD duration and EDS symptoms could have been stronger had they not been lost.

Additionally, temporality is an issue as the exposures and outcomes we analyzed here are known to be part of a vicious cycle of deterioration in PD, i.e. they influence each other longitudinally. Although we used repeated measures models, 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 in our cohort. Other potential limitations refer to no objective measures of sleep quality and structure being available, since we are relying solely on self-reported information. This is, however, the same in all studies with a large number of patients, due to feasibility constraints for using objective sleep assessments, such as polysomnography. Residual confounding due to unmeasured factors always is an unavoidable issue.

However, our regression models took into account hypothesized causal structures for each risk factor different from purely predictive approaches for insomnia and EDS in PD. One strength in our study is the population-based approach to identify PD cases, which likely yields more estimates that are more representative of all PD patients than those based on very selected clinical-based patient samples.

Future studies may want to address the possible role of circadian dysfunction in PD progression. In conclusion, we provide epidemiological evidence that both motor and non-motor dysfunction in PD are associated with sleep problems, specifically, longer PD duration, higher LED, and worse UPDRS-IA and autonomic symptoms scores are related to insomnia and EDS, while PD motor signs impact mainly insomnia. Assessment of these sleep problems in longitudinal population-based studies may be needed to help understand and manage them better and improve patients' overall health-related quality of life.

3.6 Tables and Figures

Table 3-1. Distribution of demographics, PD-related characteristics and MOS-Sleep scale scores for Insomnia and EDS, at first follow-up. PEG Study 2019.

		Mean Standardized MOS-Sleep score	
	N (%)	**Insomnia** (Mean ± SD)	**EDS** (Mean ± SD)
Total	477 (100)	0 ± 1	0 ± 1
Study cohort, PEG 1[1]	234 (49)	-0.051 ± 0.978	0.034 ± 0.978
PEG 2	243 (51)	0.049 ± 1.02	-0.033 ± 1.022
Age at interview, 65 or less	119 (25)	0.299 ± 1.139	0.04 ± 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	294 (62)	-0.001 ± 1.006	0.141 ± 1.01
Ethnicity, White	369 (77)	-0.057 ± 0.959	0 ± 0.985
Latino	79 (17)	0.183 ± 1.112	-0.059 ± 1.06
Other	29 (6)	0.228 ± 1.124	0.16 ± 1.043
Education, less than 12	69 (15)	0.259 ± 1.097	-0.037 ± 1.064
12 or more	407 (85)	-0.045 ± 0.978	0.009 ± 0.989
Age at PD diagnosis, 60 or less	128 (27)	0.284 ± 1.136	0.089 ± 1.034
more than 60	349 (73)	-0.104 ± 0.925	-0.033 ± 0.987
PD duration, 6.5 years or less	278 (58)	-0.12 ± 0.906	-0.131 ± 0.948
more than 6.5 years	199 (42)	0.168 ± 1.099	0.183 ± 1.043
Motor subtype, tremor dominant or indeterminate	140 (31)	-0.032 ± 0.939	-0.074 ± 0.969
PIGD	312 (69)	0.03 ± 1.025	0.035 ± 0.99
UPDRS-III[2] total score less than 35 (missing= 25)	350 (77)	-0.054 ± 0.957	-0.041 ± 0.951
35 or greater	102 (23)	0.235 ± 1.107	0.146 ± 1.082
Hoehn and Yahr, stages 0 to 2.5 (missing= 47)	320 (74)	-0.011 ± 0.973	-0.063 ± 0.957
stage 3 or greater	110 (26)	-0.025 ± 1.054	0.105 ± 0.991
PD medication use, dopamine agonist only (missing=3)	31 (6)	-0.289 ± 0.841	-0.2106 ± 0.702
levodopa only	254 (54)	0.017 ± 1.004	0.056 ± 1.029
both levodopa and dopamine agonist	151 (32)	0.029 ± 0.981	0.069 ± 0.959
no PD medication	38 (8)	0.025 ± 1.166	-0.405 ± 1.066
LED[3] Dopamine agonists only > 200 mg	114 (24)	0.036 ± 1.001	0.009 ± 0.929
LED Levodopa only, > 500 mg	188 (40)	0.164 ± 1.064	0.24 ± 1.046
LED Levodopa total, > 600 mg	197 (42)	0.154 ± 1.063	0.146 ± 1.039

UPDRS-IV[4] (motor complications), present	232 (53)	0.2 ± 1.051	0.041 ± 0.923
Presence of dyskinesia [5]	101 (21)	0.266 ± 1.033	0.033 ± 0.901
UPDRS-IA (non-motor, complex behaviors)[6] score > 5	114 (25)	0.45 ± 1.121	0.359 ± 0.974
Autonomic sympoms[7], score > 8	118 (25)	0.177 ± 1.051	0.331 ± 0.959
Urinary problems, present	348 (74)	0.07 ± 1.013	0.1 ± 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-I: Non-Motor Aspects of Experiences of Daily Living
UPDRS-IA (rated by physician), complex behaviors items: cognitive impairment, hallucinations, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome.
UPDRS-IB (self-completed) items: sleep problems, daytime sleepiness, pain, urinary problems, constipation, light headedness, fatigue.

7- Autonomic symptoms score: constipation, urinary, light headedness, saliva/drooling, chewing/swallowing.

Table 3-2. Linear regressions of insomnia and EDS scores on PD-related characteristics (**cross-sectional**), adjusted for sex, age and duration of Parkinson's disease in years. PEG Study 2019.

Continuous measures	**Insomnia β Coefficient[1] (95% CI)**	**EDS β Coefficient[1] (95% CI)**
PD duration, per 1 year increase	**0.06 (0.03, 0.09)**	**0.03 (0.01, 0.06)**
UPDRS-III[2] total, per 5-point increase (Total N=453)	**0.10 (0.02, 0.17)**	**0.04 (0.002, 0.08)**
UPDRS-III sub-scores, per 5-point increase, Tremor	**0.16 (0.01, 0.31)**	0.06 (-0.09, 0.21)
Rigidity	0.10 (-0.06, 0.27)	-0.01 (-0.17, 0.16)
Bradykinesia	-0.03 (-0.51, 0.44)	**0.59 (0.04, 0.97)**
Axial	0.10 (-0.03, 0.22)	**0.12 (0.004, 0.24)**
PIGD[3]	**0.32 (0.06, 0.58)**	**0.34 (0.09, 0.59)**
LED[4], per 100mg increase, Only levodopa	**0.03 (0.00, 0.06)**	**0.04 (0.01, 0.08)**
Only dopamine agonists	-0.01 (-0.03, 0.02)	-0.01 (-0.04, 0.02)
Total, Levodopa and dopamine agonists	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
UPDRS-IV[5] (motor complications) score, per 5-points increase	**0.30 (0.15, 0.46)**	0.14 (-0.01, 0.30)
UPDRS-II[7] (motor ADL) score, per 5-point increase	**0.13 (0.07, 0.20)**	**0.22 (0.15, 0.28)**
UPDRS-IA[8] (non-motor ADL) score, per 5-point increase	**0.47 (0.31, 0.63)**	**0.35 (0.19, 0.51)**
Autonomic symptoms[9] score, per 5-point increase	**0.30 (0.17, 0.44)**	**0.29 (0.16, 0.43)**
Urinary problems, per 1-point increase	**0.14 (0.06, 0.21)**	**0.13 (0.06, 0.21)**

1- Adjusted for gender, age, and duration of PD.
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- PIGD=Postural Instability and Gait Disturbance/Dysfunction/Difficulty
4- LED: Levodopa Equivalent Daily Dose
5- 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.
6- 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"
7- 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.

8- UPDRS-IA (rated by physician), complex behaviors 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

Table 3-3. Linear mixed models: association of PD-related characteristics and change in sleep problems scores across two points, on average 2.2 years apart (n=156 with follow-up). PEG Study 2019.

	Insomnia	**EDS**
	β coefficient (95% CI)	**β coefficient (95% CI)**
Model[1] for PD duration ≥ 6.5 years		
Follow-up time	0.004 (-0.037 , 0.046)	**0.004 (0.139 , 0.046)**
PD duration ≥ 6.5 years	**0.253 (0.074 , 0.432)**	**0.315 (0.139 , 0.491)**
PD duration ≥ 6.5 * time	0.039 (-0.036 , 0.114)	0.037 (-0.039 , 0.113)
Model[2] for UPDRS-III ≥ 35		
Follow-up time	0.023 (-0.055 , 0.100)	-0.038 (-0.118 , 0.042)
UPDRS-III ≥ 35	**0.275 (0.052 , 0.497)**	0.131 (-0.089 , 0.351)
UPDRS-III ≥ 35 * time	**-0.197 (-0.375 , -0.019)**	0.131 (-0.055 , 0.317)
Model[3] for LED (levodopa only) ≥ 500 mg		
Follow-up time	0.062 (-0.029 , 0.154)	0.002 (-0.093 , 0.097)
LED ≥ 500 mg	**0.231 (0.038 , 0.425)**	**0.294 (0.104 , 0.483)**
LED ≥ 500 mg * time	**-0.154 (-0.288 , -0.02)**	-0.044 (-0.186 , 0.097)
Model[4] for UPDRS-IA score ≥ 5		
Follow-up time	0.018 (-0.066 , 0.103)	0.013 (-0.075 , 0.101)
UPDRS-IA ≥ 5	**0.498 (0.286 , 0.710)**	**0.378 (0.170 , 0.586)**
UPDRS-IA ≥ 5 * time	-0.113 (-0.267 , 0.041)	-0.131 (-0.293 , 0.031)
Model[4] for autonomic symptoms score ≥ 8		
Follow-up time	0.021 (-0.06 , 0.101)	0.006 (-0.078 , 0.091)
Autonomic symptoms score ≥ 8	**0.196 (-0.029 , 0.421)**	**0.324 (0.105 , 0.544)**
Autonomic symptoms ≥ 8 * time	**-0.211 (-0.371 , -0.051)**	-0.126 (-0.296 , 0.044)

1- Adjusted for sex and time-varying age
2- Adjusted for sex and time-varying age and PD duration
3- Adjusted for sex and time-varying: age, PD duration, and UPDRS-III
4- Adjusted for sex and time-varying: age, PD duration, UPDRS-III, and LED

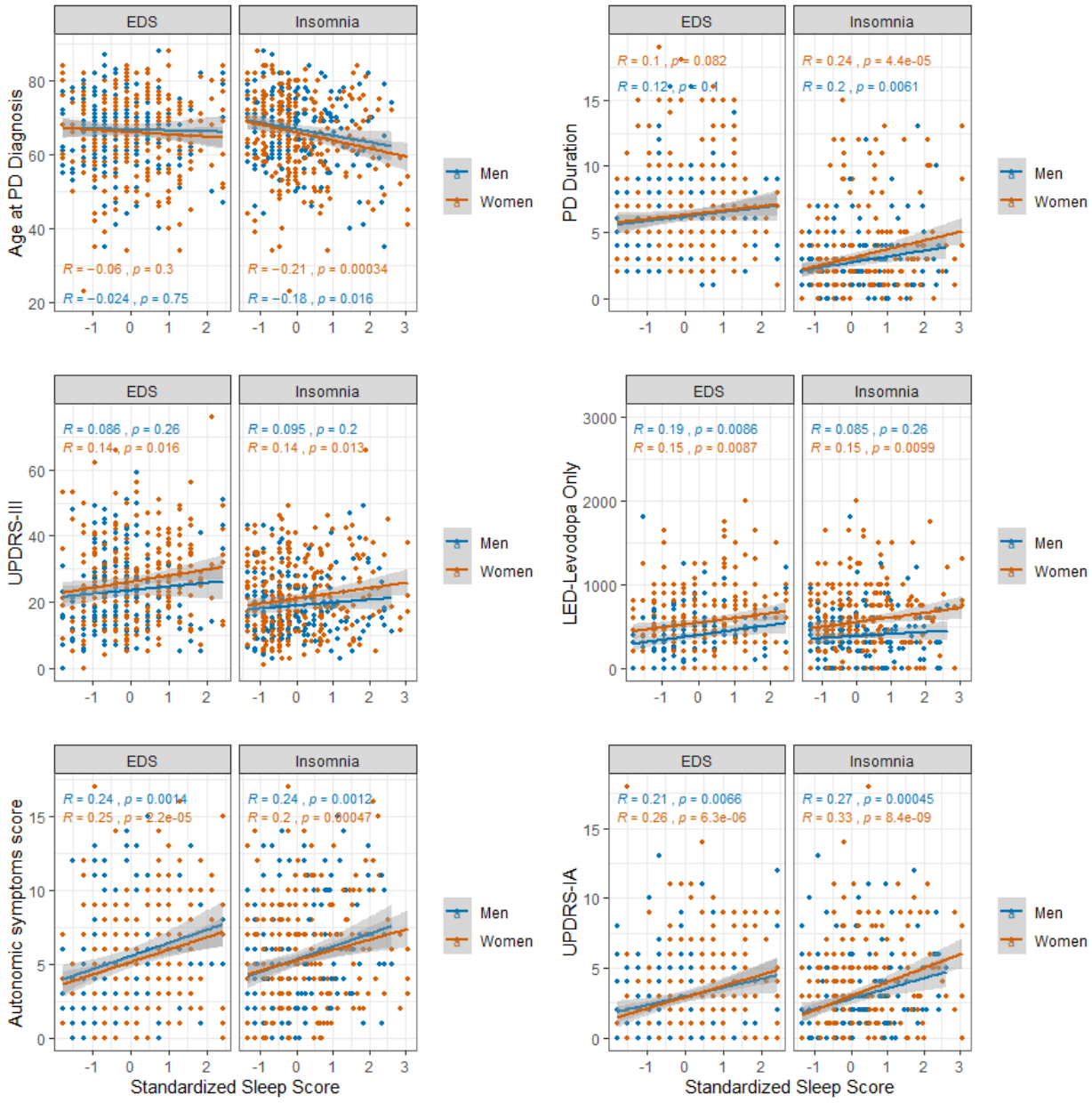


Figure 3-1. Scatterplot of standardized sleep scores (mean 0, SD 1) by PD characteristics stratified by gender. Including best fit linear correlation line and Pearson correlation coefficients and p-values. PEG Study 2019.

Table S3-1. Distribution of demographics, PD-related characteristics and MOS-Sleep scale for the group followed compared to the group lost to follow-up. PEG Study 2019.

	Followed		Lost to follow-up		
	N or mean	(SD or %)	N or mean	(SD or %)	p-value[1]
Total number	156	(100)	321	(100)	
Study cohort, PEG 1	156	(100)	78	(24)	
PEG 2	0	0	243	(76)	
Age at interview, years	71.9	(9.4)	72.7	(9.8)	0.39
Gender, men	95	(61)	199	(62)	0.82
Age at PD diagnosis, years	66.9	(9.8)	65.8	(10.4)	0.27
PD duration, years	5.0	(2.6)	6.9	(2.9)	<.0001
Motor subtype, Tremor Dominant or indeterminate	52	(34)	88	(29)	0.32
PIGD	101	(66)	211	(71)	
UPDRS-III total score	23.4	(10.1)	26.1	(13.4)	0.01
UPDRS-III sub-scores, tremor	3.4	(2.5)	3.5	(3.2)	0.64
Rigidity	3.6	(2.5)	4.1	(3.0)	0.03
Bradykinesia	1.6	(1.0)	1.5	(1.0)	0.48
Axial	5.4	(3.0)	6.1	(4.4)	0.06
PIGD	1.8	(1.4)	1.9	(2.0)	0.40
Hoehn and Yahr stage, average	2.4	(0.7)	2.4	(0.8)	0.38
Dopamine agonist any, yes	75	(48)	102	(32)	0.00
LED dopamine agonists only, mg	352	(785.0)	261	(193.0)	0.33
Levodopa, yes	135	(87)	270	(85)	0.64
LED Levodopa only, mg	569.0	(283.0)	568.0	(325.0)	0.96
UPDRS-IV (motor complications), score	2.1	(2.9)	2.5	(3.2)	0.26
Presence of dyskinesia	30	(21)	66	(22)	0.74
UPDRS-IA (non-motor, complex behaviors) score	2.7	(2.5)	3.1	(3.1)	0.13
UPDRS-IB (non-motor) score	8.7	(4.7)	10.1	(4.9)	0.01
UPDRS-II (motor ADL) score	12.2	(7.3)	16.2	(9.1)	<.0001
Autonomic symptoms score	4.4	(3.2)	5.7	(3.5)	0.00
Urinary problems, item score	1.3	(1.2)	1.5	(1.2)	0.10
MOS Sleep scale, Sleep Somnolence (**EDS** measure)	43.4	(21.5)	41.9	(24.8)	0.50
Sleep Disturbance (**Insomnia** measure)	28.7	(22.6)	31.4	(23.5)	0.20
Snoring	37.4	(32.0)	33.1	(29.3)	0.19
Shortness of breath	10.5	(21.4)	9.8	(19.3)	0.73
Sleep Adequacy [2]	58.7	(25.6)	56.1	(27.7)	0.32

1- p-value for testing equality of means (t-test) or proportions (chi-square) between groups followed and not followed

2- Higher score is better sleep adequacy

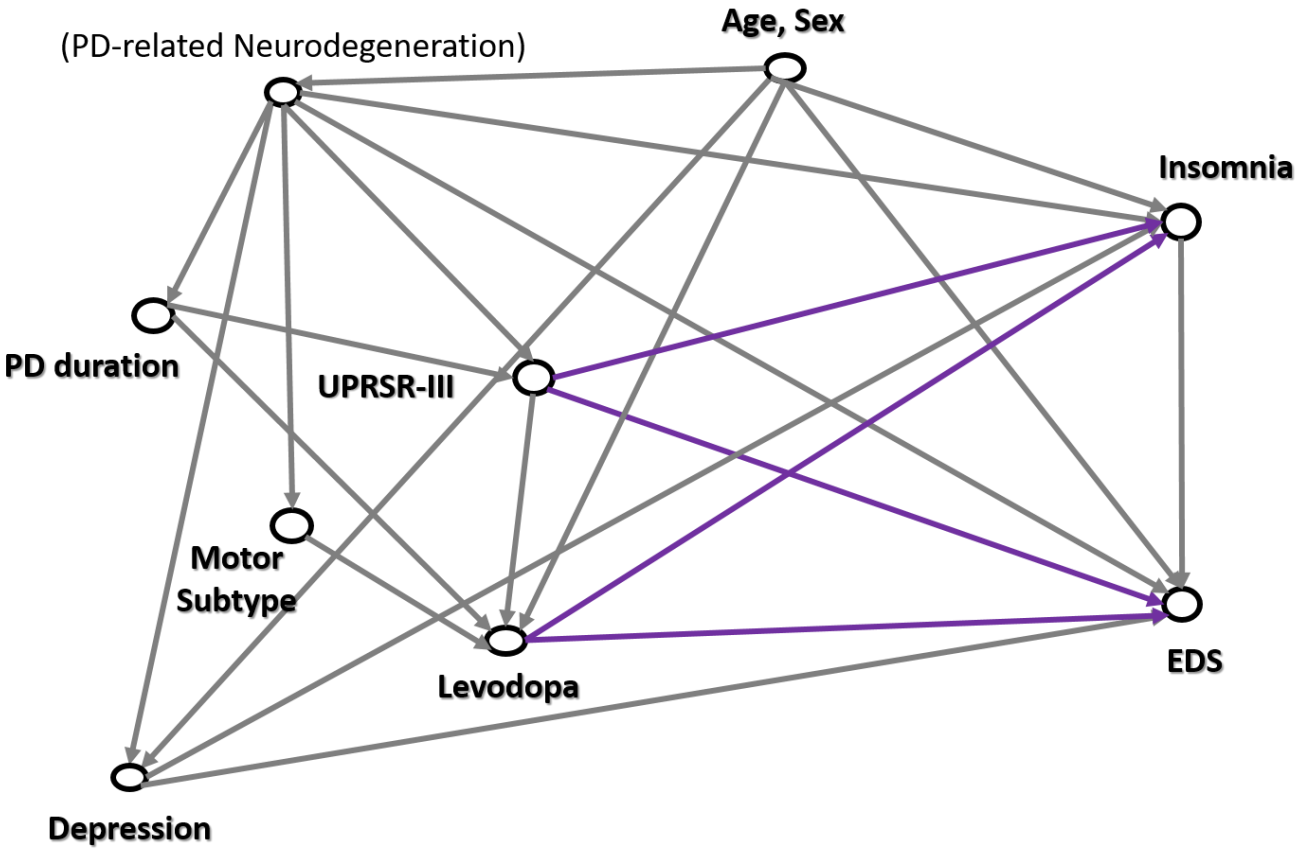


Figure S3-1. Proposed Directed Acyclic Graph (DAG) depicting hypothesized relation of factors considered in cross-sectional analyzes (arrows in purple). Variables in parenthesis are not measured. UPDRS-III= measure of motor dysfunction severity. EDS= excessive daytime sleepiness.

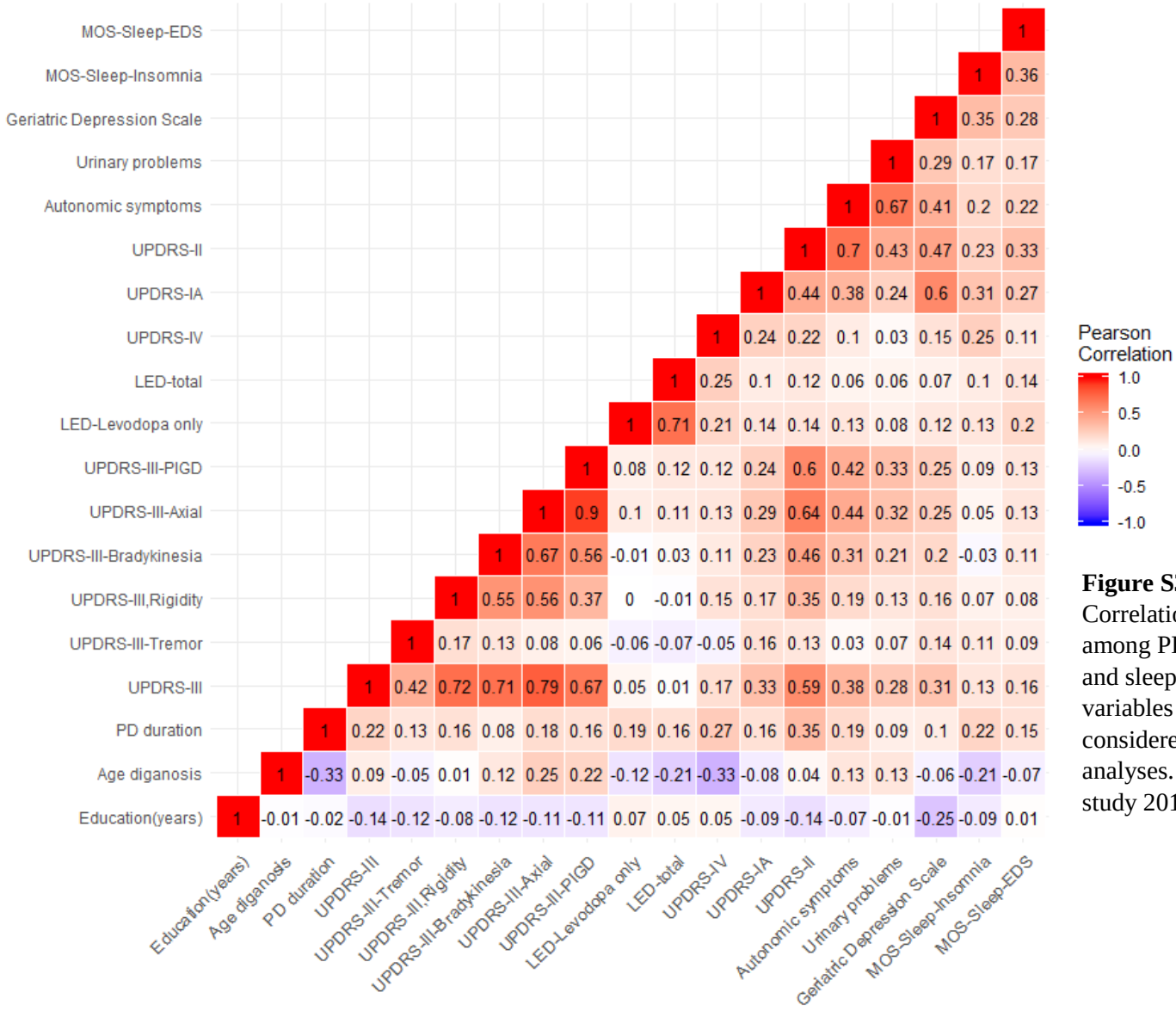


Figure S3-2. Correlations among PD-related and sleep variables considered in analyses. PEG study 2019.

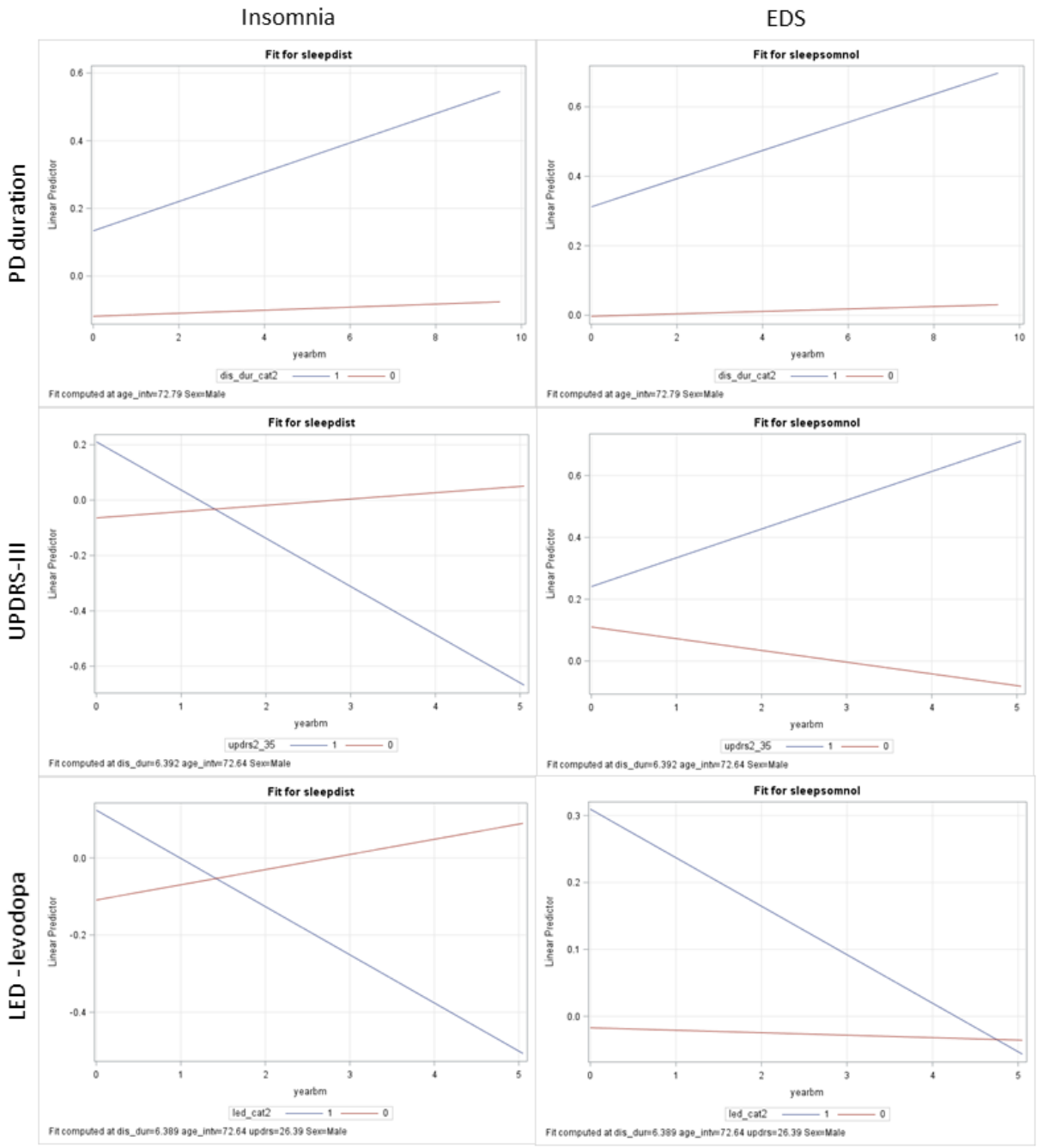


Figure S3-3. Plots of predicted values from linear mixed models fixed-effects coefficients depicted in Table 3-3. PEG Study 2019
y-axis: standardized predicted sleep scores, x-axis: years of follow-up
Red lines: PD duration <5 years, UPDRS-III < 35, LED< 500mg.
Blue lines: PD duration ≥5 years, UPDRS-III ≥ 35, LED≥ 500mg.

4 Depression and Anxiety Affect Insomnia and Excessive Daytime Sleepiness in Community-based Parkinson's Disease Patients

4.1 Abstract

Introduction: Mood disorders including depression and anxiety are common in Parkinson's disease, and may increase risk of other health problems such as sleep disturbances. Here, we further explore the role of historical diagnoses of depression and anxiety prior to PD onset and their treatments as well as current depressive symptoms on prevalent insomnia and EDS symptoms in PD patients.

Methods: Sleep symptoms were measured with the MOS-Sleep questionnaire in 477 PD patients of a community-based cohort, at an average of 6.3 years since PD first diagnosis, and for a sub-group of 156 patients, another sleep measure was available at an average 8.5 years of PD duration. We estimated adjusted mean differences in insomnia and EDS scores according to neuropsychiatric diagnoses categories taken at cohort baseline. Linear mixed models were used to estimate influence of depression symptoms to worsening in sleep symptoms.

Results: Average MOS-Sleep EDS score was 42.2± 23.7 and insomnia score, 30.5± 22.6. In women, anxiety or depression (mean difference: 13.8; 95% CI 5.5, 22.0) diagnosis occurring 10+ years before PD contributed most strongly to insomnia scores, compared to never diagnoses. While in men, depression or anxiety diagnosed in prodromal or clinical stages of PD (<10 years before PD diagnosis) contributed to insomnia symptoms (8.0; 95% CI 1.8, 14.2) and to EDS (9.4; 95% CI 2.4, 16.3). Current depression treatment and symptoms were strongly associated with EDS in men than women. In longitudinal models, mood symptoms (GDS scores) at the

time of our first sleep measure, about 6 years after a PD diagnosis, were not associated with worsening sleep symptoms over time.

Discussion: Although insomnia and EDS result of a complex interaction of lifestyle and clinical factors that can be PD-related or not, we provide evidence, in the largest community-based evaluating sleep in PD, that mood disorders diagnosis history and symptoms contribute to prevalent insomnia and EDS symptoms in PD patients. In men, depression related to PD is associated with EDS and in women, mood disorders are less related to PD and their sleep consequences are mainly insomnia symptoms.

4.2 Introduction

Parkinson's disease (PD) is widely known for its motor manifestations, mainly tremor at rest, rigidity, bradykinesia, and postural instability, but in the past decade a wide range of non-motor features have been acknowledged as being a part of the PD syndrome across all stages of disease progression. Mood disorders and sleep problems are important non-motor symptoms in PD, but they also affect the general population and are highly prevalent among older adults (Kay, Tanner, & Bowers, 2018; Larsen, Dalen, Pedersen, & Tysnes, 2017; Tholfsen et al., 2015). Thus, it is of interest to understand better what PD-specific contributions to these features are and what the most appropriate treatment options may be.

The most common mood disorders in PD are depression and anxiety, and they greatly affect activities of daily living and health-related quality of life. For example, sleep problems, mainly insomnia-related symptoms and excessive daytime sleepiness (EDS), are important potential consequences of depression and anxiety, and may conversely further worsen these disorders. In

PD patients, the most common sleep problems are insomnia, EDS, and REM Sleep Behavior Disorder (RBD). We have previously reported that RBD features predict faster progression of motor and cognitive symptoms in PD (Duarte Folle, Paul, Bronstein, Keener, & Ritz, 2019), and we also found that PD motor and other non-motor clinical features contribute to insomnia and EDS. Specifically, motor symptoms related to postural instability and gait difficulty, high levodopa doses, and autonomic symptoms were associated with both more insomnia and EDS scores. Also, motor symptoms related to tremor and motor complications were only associated with insomnia symptoms, while bradykinesia was strongly associated with EDS. Interestingly, this later association did not hold up when we adjusted for concurrent depressive symptoms. Here, we will further explore the role of neuropsychiatric disorders and their treatment on the occurrence of EDS and insomnia in PD.

Clinical and epidemiological studies using predictive approaches have assessed risk factors for sleep problems in PD, but results are not consistent across them, likely because in some, patients were selected from specialty clinics, other studies were too small, most did not account for confounding factors when addressing specific hypotheses, and finally, sleep problems, depression and anxiety definitions were very heterogeneous. For example, some studies reported cross-sectional associations for depressive symptoms with EDS and insomnia, such as the ParkWest population-based study of 153 PD patients from Norway (Gjerstad et al., 2007; Tholfsen et al., 2015), and the clinical-based PROPARK study, which assessed 413 patients in the Netherlands (K. Zhu et al., 2016b, 2016a). These studies did not measure anxiety. On the other hand, a small clinical study of 90 patients from Brazil did not find depression or anxiety to be associated with insomnia (Sobreira-Neto et al., 2019), and a large cross-sectional study of

1,221 PD patients from an outpatient clinic in China did not find depression to be associated with EDS (Xiang et al., 2019). Some of these previous studies have assessed sleep problems longitudinally, but results were no less inconsistent. Not much is known about how mood disorders may affect EDS and insomnia or vice versa during PD progression or at specific points in the clinical course, such that it would suffice to treat depression to address these sleep disorders as well, or whether treatment of sleep disorders may mitigate mood disorders in PD.

Thus, more comprehensive assessments of neuropsychiatric disorders and sleep disturbances common among PD patients may suggest preventive and treatment options. To address some of these knowledge gaps and inconsistencies across previous studies, here we will estimate the contributions that historical diagnoses of depression and anxiety prior to PD onset and their treatments as well as current depressive symptoms have on prevalent insomnia and EDS symptoms in PD patients cross-sectionally, and also assess the contributions of baseline depressive symptoms to longitudinal changes in insomnia and EDS after two years of follow-up, in a population-based cohort of PD patients.

4.3 Methods

Research Ethics

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.

Study design

The Parkinson's Environment and Genes Study (PEG), identified new-onset (up to 5 years after diagnosis) PD cases in two rounds enrolling patients at baseline from 2001 to 2007 and 2011 to 2017 (PEG 1 & PEG 2), from the entire population of three California counties. PEG 1 participants were seen up to four times during follow-up, on average 3.2 years apart. For most PEG 2 participants, there has only been one follow-up thus far, on average 3.3 years after baseline enrolment. At all visits, participants in both studies were examined by movement disorders specialists affiliated with UCLA to confirm diagnosis of idiopathic PD, to evaluate motor signs and UPDRS scores (in 2016 we adopted the MDS-UPDRS), and record their Hoehn and Yahr stage.

At all visits, participants also completed an interview in which their medical history was recorded with assistance of trained research assistants and information such as demographics, lifestyle, occupational, and household exposures was ascertained. The medical interview asked whether the patient had ever been told by a doctor that they have a type of disease or disorder (and at which age), including for example, high blood pressure (HBP), diabetes, depression, and anxiety, and whether they had ever taken medications for common conditions for more than two weeks and – if yes – between which ages. At all study visits, participants also self-completed a Geriatric Depression Scale (GDS), some participants may have gotten assistance from caregiver or research assistants if necessary. A more detailed non-motor and psychosocial assessment which comprised of different standardized surveys was used only at study follow-up visits and included questions about sleep quality.

Measure of outcomes: insomnia and EDS

We adopted the Sleep Survey of the Medical Outcomes Study (MOS-Sleep) as the assessment tool for symptoms of insomnia and EDS in our study. This questionnaire was part of a more detailed assessment of non-motor symptoms and was only used during follow-up visits. Thus, the first MOS-Sleep measure in this study was available on average 6.3 years after an initial PD diagnosis had been made.

The MOS-Sleep scale has twelve items, each with six answer options on a Likert scale, and measures subjective experiences related to sleep in the last four weeks across several domains: sleep initiation or maintenance, sleep quantity and perceived adequacy, somnolence, and respiratory problems. The instrument's content is very similar to two questionnaires widely used in sleep and PD research, the Pittsburgh Sleep Quality Index (PSQI) and the Parkinson's Disease Sleep Scale (PDSS) (Chaudhuri et al., 2002). The PSQI also elicits symptoms experienced in the past four weeks, while the PDSS asks for recall over the past week only and includes three additional items focused on motor dysfunction (such as presence of tremor at awakening). The MOS-Sleep has been validated in and used to study populations with chronic diseases other than PD and will allow us to compare findings in PD patients with other populations. Its items are summarized to create five scores (Sleep Disturbance, Somnolence, Sleep Adequacy, Snoring, and Shortness of Breath), each ranging from 0 to 100, and it also collects average time to fall asleep (sleep latency) and average sleep duration.

As our measure for insomnia, we used the MOS derived continuous score 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). For EDS, we used the MOS-Somnolence score (items: drowsy during day, having trouble staying awake during the day, take naps).

Measures of depression, anxiety, medication, and other covariates

Information on diagnosis and treatment of depression, anxiety and other co-morbidities were taken from the Medical Questionnaire. In an attempt to distinguish between diagnosed mood disorders related to or independent of prodromal PD, we used a lag of ten years or more between a diagnosis of depression or anxiety and a diagnosis of PD. This approach was previously applied in the PEG study (Jacob, Gatto, Thompson, Bordelon, & Ritz, 2010). As also done previously, we relied on the following as our measure of mood disorders: the presence of a diagnosis of anxiety or/and depression or/and having taken anxiety or depression medications with or without a diagnosis. Psychotropic medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system, and we included Anxiolytics (ATC code: N05B), Hypnotics and Sedatives (N05C), and Antidepressants (N06A).

We used GDS scores as a measure of current depressive symptoms. This scale has fifteen items and a higher score indicates more symptoms (Lopez et al., 2018). We used a cut-off of seven points to indicate the presence of depression, but also considered cut-offs of five or ten points in sensitivity analysis, as done previously (Jacob et al., 2010).

Apart from information on motor disability obtained at our neurological examination at each study visit, we also have available lifestyle information from baseline including information on smoking, alcohol, and caffeine use history, and body mass index (BMI). Finally, we used data

from standardized instruments applied at follow-up visits to measure sleep apnea (Berlin Questionnaire), social support, stressful life events, perception of health care quality, and quality of life (SF-36, EQ-5D). Social support was measured with the five-item form of the MOS Social Support Scale, with high social support defined, as previously published (Rod, Bordelon, Thompson, Marcotte, & Ritz, 2013), when patients reported all or most of the time to have someone available for support, in at least four of the five items. Information on fourteen stressful life events and emotional distress associated to these from PD diagnosis until first follow-up, was collected using a modified version of the Social Readjustment Rating Scale (Rod et al., 2013), and we dichotomized this scale at 3+ upsetting events. Dopaminergic medication use was recorded as previously described as Levodopa Equivalent Dose (LED).

Statistical analysis

We conducted analyses in statistical software package SAS (SAS 9.4, SAS Institute, Cary, NC) version 9.4 and generated figures in R. Insomnia and EDS scores were approximately normally distributed in univariate and multivariate analyses for continuous factors.

Due to a lack of studies reporting on cut-off scores for the MOS-Sleep scales, we chose not to dichotomize the insomnia and EDS outcomes, but categorized the characteristics described in Table 4-1, including demographics and PD clinical information to describe means (and standard deviations) for insomnia and EDS scores across categories. To visualize how insomnia and EDS scores were distributed across other sleep characteristics, we used boxplots, and to display how depressive symptoms correlate with sleep symptoms, we plotted concurrent GDS versus sleep

scores by medication use status, for men and women separately, and estimated Pearson correlation coefficients.

We estimated MOS-Sleep scores using linear regression models, adjusting for potential confounders including gender, age at interview and PD duration to generate adjusted mean difference estimates when comparing the presence or absence of mood disorders. Using linear regression models to predict mean adjusted EDS and insomnia scores and 95% confidence intervals, we also estimated associations with co-morbidities and lifestyle characteristics, as displayed in bar plots. In order to estimate the potential effect of measures taken at baseline, including depression, anxiety, medications, co-morbidities and lifestyle, on sleep scores, we used Inverse Probability of Censoring Weighting (IPCW) to account for the lack of information about sleep outcomes in those of participants from baseline (44%) who were never seen at follow-up. Weights were generated conditional on presumed determinants of loss to follow-up: age, gender, PD duration, UPDRS motor and MMSE scores.

In longitudinal linear mixed models, we predicted changes in insomnia and EDS scores over two years of follow-up according to depression measured by GDS scores above 7 points. We used random intercept and slope, and compound symmetry covariance structure in these models.

4.4 Results

The 477 patients who provided MOS-Sleep scale data at least once (on average 6.3 ±3.0 years after first PD diagnosis), were mostly male (62%) and white (77%). The average EDS score was 42.2± 23.7 and the insomnia score 30.5± 22.6 (Table 4-1), and these scores were only

moderately correlated with each other (Pearson correlation coefficient= 0.34 p< 0.0001). Insomnia scores were similar in men and women (30.2 and 30.6), but EDS was higher in men (45.5 and 37.1) (Table 4-1). Insomnia scores were worse in patients younger than 65 years, and also slightly worse in Latino patients and in those with less than 12 years of education. As previously described those with a UPDRS-III≥ 35 had higher insomnia scores, while patients with a higher LED had higher EDS scores.

Those participants with sleep latency greater than 60 minutes, and those with sleep duration less than six hours had – as we would expect – worse insomnia scores (see Figure 5-11). Those with probable RBD or at high risk for sleep apnea, measured with the Berlin scale, had higher scores for EDS. However, these results are only crude, and when stratified by men and women, are not present anymore (results not shown). A history of high blood pressure, a diagnosis of type 2 diabetes, and a history of traumatic brain injury (with unconsciousness) were all positively associated with insomnia scores, but none of these disorders was associated with EDS scores (Figure 5-2). Lifetime consumption of coffee, alcohol and smoking also increased insomnia symptoms (Figure 5-2) but not EDS. Health related quality of life (SF-36 score) was strongly correlated with both insomnia and EDS scores (see scatterplots Figure 5-3), in men and women.

Neuropsychiatric-related diagnoses

A total of 182 (38%) patients reported having ever received a diagnosis of depression, of whom 117 (64%) received a PD diagnosis within less than 10 years (Table 4-1). An anxiety diagnosis was reported by 158 patients (33%) and of these, 109 anxiety diagnoses (69%) were received less than 10 years before the PD diagnosis. In general, those with diagnosis of depression or

anxiety at any time, had higher EDS and insomnia scores after on average six years with PD than those who had never been diagnosed with a mood disorder (Table 4-1). Men and women reported similar frequencies for a depression diagnosis (34% for men, 37% for women), while women (34%) were slightly more likely to have been seen for anxiety than men (27%).

In general, a diagnosis of depression was associated with worse insomnia symptoms only in women, especially when depression was diagnosed more than ten years before PD; i.e. was more likely unrelated to prodromal PD. In models adjusted for age and duration of PD, the mean difference estimates for insomnia scores, comparing those with a diagnosis of depression within 10 years before PD to those without a depression diagnosis at any time, was 20.1 (95% CI 11.4, 28.8) (Table 4-2). An anxiety diagnosis was associated with insomnia in men and women, but interestingly, there were differences in terms of when this diagnosis was received in relation to a PD diagnosis. Anxiety diagnoses 10+ years before PD (likely not prodromal PD), like depression, predicted insomnia scores in women (adjusted mean difference comparing to never anxiety: 11.4, 95% 1.3, 21.5), but not in men (adjusted mean difference: 2.4, 95% CI -4.3, 9.1). Interestingly, a more recent diagnosis of anxiety (<10 years before a PD diagnosis, i.e., in prodromal stages of PD), predicted insomnia scores only in men, with an adjusted mean difference of 10.2 (95% CI: 3.1, 17.3).

A depression diagnosis was more strongly associated with EDS scores than an anxiety diagnosis (Table 4-3). The mean difference in EDS scores for ever diagnosis of depression compared to never, adjusted for gender, age, duration of PD and UPDRS-motor score, was 8.4 (95% CI: 3.7, 13.1) and for anxiety, 4.0 (95% CI: -0.8, 8.7) (Table 4-3). Use of antidepressant medication was

a weaker predictor of EDS than a depression diagnosis, ever compared to never use was associated with on average 6.2 (95% CI 1.8, 10.5) higher points in EDS scores.

The psychiatric medication class most reported by our PD cohort at the time sleep symptoms were first measured (mean of 6 years of PD) were selective serotonin reuptake inhibitors (SSRIs) (n=92), followed by benzodiazepines (n= 64), while very few patients used non-selective monoamine reuptake inhibitors (n=7) (Table 4-2). Current use of psychiatric medications was not associated with differences in insomnia scores (Table 4-2). For EDS, current use of antidepressants in men, specifically SSRIs, was associated with worse EDS scores, the adjusted mean difference was 9.5 (95% CI 2.8, 16.1).

Low social support and low perception of health care quality were associated with higher insomnia scores in both men and women (Table 4-2), but not with EDS scores (Table 4-3). More than three stressful life events predicted higher insomnia and EDS symptoms only in men, the adjusted mean difference for insomnia (compared to less than three life events) was 12.0 (95% CI: 6.8, 17.2) (Table 4-2), and for EDS, 7.7 (95%CI: 2.0, 13.4) (Table 4-3).

Concurrent depression symptoms measured by the GDS continuous score were positively correlated with both insomnia and EDS symptoms (see scatterplot figures 4-4). Use of psychiatric medication seemed to slightly improve both depression and EDS symptoms, shown by smaller slopes and correlation coefficients for those using medication. However, correlations of insomnia symptoms and GDS were similar between groups of current medication users and non-users. In linear regression models adjusted for gender, age and PD duration, these

associations persisted. A 1-point increase in GDS score was associated with an average increase of 2.2 (95% CI 1.6, 2.8) points in insomnia scores, including for those who used psychiatric medications. While the associated increase with EDS score by GDS was slightly reduced comparing strata of current psychiatric medication users and non-users, though it was still present (i.e., from 1.9; 95% CI 1.2, 2.5 to 1.3; 95% CI 0.4, 2.3).

For 156 patients from the first recruitment period (PEG 1), a second sleep assessment was available on average 1.8 years after the first was obtained. Within-persons EDS scores increased on average by 3.0 (95% CI -0.7, 6.6) points over follow-up. When stratifying according to GDS score, for those with a GDS< 7 at the time of the first sleep measure, within-person EDS scores increased on average by 3.8 (95% CI 0.1, 7.6), while for those with GDS≥ 7, EDS scores did not change significantly with additional follow-up (-1.2, 95% CI -12.7, 10.2). Insomnia scores did not change significantly over time (on average -1.4 (95% CI -4.6, 1.8) points). In linear mixed models adjusted for gender, time-varying age, and PD duration higher depression scores were only associated with higher scores for sleep dysfunction at the first time we measured these (see main effects for GDS≥ 7 in Table 4-4). We did not observe a change in sleep scores over time for those with a GDS≥ 7 at first measurement (the interaction term between GDS≥ 7 and follow-up time was not statistically significant).

4.5 Discussion

In this large population-based cohort of Parkinson's disease patients we assessed associations of depression and anxiety diagnoses, current depressive symptoms and mood disorder and sleeping medication treatments with prevalent insomnia and EDS symptoms, on average within 6.3 years

after a first diagnosis of PD. Overall, a history of depression and anxiety diagnoses predicted prevalent symptoms of insomnia, while depression was more strongly associated with EDS than anxiety. In women, anxiety or depression diagnosis occurring 10+ years before PD contributed most strongly to insomnia symptoms, while in men it was depression or anxiety diagnosed in prodromal or clinical stages of PD (<10 years before PD diagnosis). Interestingly, we also observed in longitudinal models, that worse mood symptoms (GDS scores) at the time of our first sleep measure, about 6 years after a PD diagnosis, were not associated with worsening sleep symptoms over time.

While MOS Sleep scores have not been reported in other PD studies, we are able to compare these with general population samples. Our study population had higher scores (30.5 for insomnia and 42.4 for EDS) than previously reported for a representative sample of the US general population (mean age of 46 years; age range 18 to 94), that was 51% female and a mostly White (mean scores: insomnia: 24.5 and EDS: 21.9) (Hays et al., 2005). We also found higher MOS Sleep EDS scores in our PD patients compared with a sample of 173 participants in a clinical trial for neuropathic pain (mean 35.3), with an average age closer to our population, i.e. 72 years (range 31-100 years), 53% female and mostly White; yet, insomnia scores were reported to be higher in this clinical sample (mean 37.3) than in ours (Hays et al., 2005).

In our cohort, as in several previous studies evaluating EDS in PD (Tholfsen et al., 2015; K. Zhu et al., 2016a), we observed worse EDS symptoms in men than in women, though nobody has given an explanation for this difference thus far. We also show that depression drives EDS symptoms in men, and the estimates further strengthened when we adjusted for UPDRS motor

scores, while depression diagnosis was associated with insomnia symptoms only in women. Following what we observed for depression and anxiety diagnosis, in women, concurrent depression symptoms measured by GDS scores were highly positively correlated with insomnia, but had a smaller correlation with EDS. On the contrary, in men, concurrent depressive symptoms were highly correlated with EDS.

Two previous studies (Lopez et al., 2018; Perrin et al., 2017) discussed that depression in PD predominantly manifests as somatic symptoms, for example, fatigue, apathy, and insomnia, and less as typical affective depressive symptoms, such as anhedonia, but it is important to note that previous studies of PD enrolled mostly men. A clinical study of 307 patients from Canada assessed gender differences in depression in PD and found that men with PD may have more physical symptoms of depression including loss of libido and fatigue, while in women with PD common features of depression are related to anxiety, such as worthlessness, irritability, agitation, and self-dislike. Thus, EDS may be a specific somatic manifestation of depression in men with PD, which could in part explain the frequently described association of EDS in PD with male gender.

On the other hand, insomnia may be a more important manifestation of general mood disorders independent of PD in women. This is suggested by the timing of diagnosis of depression and anxiety prior to PD diagnosis for insomnia and EDS in women (i.e. 10+ years before PD diagnosis), while in men, mood disorder diagnoses occurred more closely in time to PD (i.e. seem to be part of the prodromal PD syndrome). We previously reported for our PEG 1 cohort that women had a greater incidence of depression in early adult life (Jacob et al., 2010) as

compared with men. We now also observe that this has a negative influence on sleep symptoms including insomnia and EDS later in life, at an average of six years of PD duration. This suggests that, in women with PD, it may be important to treat sleep disorders as part of generalized depression rather than considering it simply a non-motor feature of their PD.

In our study, 17% of patients used a hypnotic, sedative or anxiolytic medication at the time we assessed sleep, and the most common class was benzodiazepines. This is consistent with previous clinical-based studies: in the PROPARK study (K. Zhu et al., 2016b), 17% of patients used sleep medications, and in the Parkinson's Progression Markers Initiative (Amara et al., 2017), an international multi-center cohort of 423 PD patients, 18% of patients used sedatives. Current antidepressant use was reported for 26% of our participants, and the most common class was SSRIs. None of the current medications were associated with insomnia symptoms, possibly indicating that these medications were indeed effective for insomnia, while concurrent antidepressant use was associated with higher EDS scores only in men, supporting the hypothesis that worse depression symptoms in men with PD manifest as EDS, but also potentially showing that EDS does not respond to pharmacotherapy for depression.

Whereas in cross-sectional analyses worse depression symptoms predicted worse sleep symptoms, GDS did not predict significant changes in EDS or insomnia scores over two years of follow-up in mixed models adjusted for gender, PD duration, age, UPDRS motor and LED. The Parkinson's Progression Markers Initiative (Amara et al., 2017) study has been the only longitudinal study to find an association of depressive symptoms and EDS incidence, but these results refer to the first three years after PD diagnosis only. In the PROPARK study, which

evaluated patients at baseline on average at ten years of PD duration, depression symptoms measured with the Hamilton Scale were not associated with EDS incidence after five years of follow-up.

Association of RBD and sleep apnea with EDS had been previously reported (Zhou et al., 2014). Even though we also found the mean crude scores for EDS to be higher in those with RBD and in those with high risk for apnea, when we stratified by gender, we observe that this is probably confounded, since men have more RBD and higher risk prevalence of snoring, as well as EDS, as discussed. No other studies had shown how other common co-morbidities and lifestyle factors may influence sleep problems in patients with PD. We show that only insomnia symptoms, and not EDS, is negatively affected by previous diagnosis of hypertension and diabetes, as well as by higher lifetime consumption of coffee and smoking, indicating that insomnia may also result from more diverse components of health, in addition to mood and PD-related symptoms.

All measures of sleep and mood disorders diagnoses and symptoms we used were self-reported. Objective measures of sleep quality and structure including polysomnography with multi latency test to assess excessive sleepiness are impractical in large community-based studies. After our cohort baseline, about 40% of patients were not seen for a follow-up, so no information on sleep symptoms was collected. But in the estimates calculated for risk factors measured at cohort baseline, we attempted to model loss to follow-up to be independent of a few assumed measured factors, including age, PD duration, motor UPDRS motor, MMSE, and risk factors evaluated (e.g. depression and anxiety diagnoses), using IPCW. Additional strengths in our study include

that patients were evaluated by movement disorders specialists to confirm idiopathic PD and to measure motor signs.

Future studies could re-examine our findings assessing sleep symptoms early in PD course, potentially evaluating if early interventions and new approaches for mood disorders can improve sleep later in PD, and how these may affect motor and cognitive disease progression. In conclusion, although insomnia and EDS result of a complex interaction of lifestyle and clinical factors that can be PD-related or not, we provide evidence, in the largest community-based evaluating sleep in PD, that mood disorders diagnosis history and symptoms contribute to prevalent insomnia and EDS symptoms in PD patients, and that these relations may have different features in women and men with PD. Specifically, depression related to PD is associated with EDS in men, while, in women, mood disorders are less related to PD and their sleep consequences are mainly insomnia symptoms.

4.6 Tables and Figures

Table 4-1. Distribution of characteristics for PD patients at first sleep measure, and Insomnia and EDS scores by patients' characteristics. PEG Study 2019.

	N (%)	Insomnia score Mean (SD)	EDS score Mean (SD)
Total	477 (100)	30.5 ± 22.6	42.4 ± 23.7
Study cohort, PEG 1	234 (49)	29.4 ± 22.1	43.2 ± 23.2
PEG 2	243 (51)	31.7 ± 23.1	41.6 ± 24.3
Age at interview, < 65	119 (25)	37.3 ± 25.8	43.4 ± 24.4
65 to 80	263 (55)	28.1 ± 20.3	42.1 ± 22.3
≥ 80	95 (20)	28.8 ± 23.2	42.1 ± 27
Gender, women	183 (38)	30.6 ± 22.5	37.1 ± 22.4
men	294 (62)	30.5 ± 22.8	45.8 ± 24.0
Ethnicity, White	369 (77)	29.2 ± 21.7	42.4 ± 23.4
Latino	79 (17)	34.7 ± 25.2	41.0 ± 25.2
Other	29 (6)	35.7 ± 25.4	46.2 ± 24.8
Years of education, < 12	69 (15)	36.3 ± 24.8	41.5 ± 25.3
≥ 12	407 (85)	29.5 ± 22.1	42.6 ± 23.5
Age at PD diagnosis, < 60	128 (27)	37.0 ± 25.7	44.5 ± 24.6
60 to 75	266 (56)	28.7 ± 20.8	42.7 ± 22.2
≥ 75	83 (17)	26.5 ± 21.5	38.3 ± 26.7
PD duration, years, < 5	201 (42)	27.3 ± 20.4	39.0 ± 23.3
6 to 9	230 (48)	30.9 ± 23.0	44.7 ± 24.6
≥ 10	46 (10)	43.2 ± 25.9	45.9 ± 19.8
Motor subtype, PIGD	312 (69)	29.8 ± 21.3	40.7 ± 23
Tremor Dominant or Indeterminate	140 (31)	31.2 ± 23.2	43.2 ± 23.5
UPDRS-III < 35 (total N=452)	350 (78)	29.3 ± 21.7	41.4 ± 22.6
≥ 35	102 (23)	35.9 ± 25.1	45.9 ± 25.7
Total daily LED, < 600 mg	299 (63)	28.1 ± 21.3	40.2 ± 22.8
≥ 600 mg or more	175 (37)	34.0 ± 24.1	45.8 ± 24.7
Depression diagnosis, ever	182 (38)	37.1 ± 22.8	49.4 ± 23.9
never	295 (62)	27.9 ± 22.0	39.6 ± 23.1
Depression diagnosis, < 10 years before PD	117 (28)	35.9 ± 24.1	48.6 ± 24.3
≥ 10 years before PD	62 (17)	38.5 ± 21.3	50.4 ± 24.0
Anxiety diagnosis, ever	158 (33)	37.3 ± 24.1	46.7 ± 22.6
never	319 (67)	28.2 ± 21.7	40.9 ± 24.0
Anxiety diagnosis, < 10 years before PD	109 (25)	37.1 ± 25.6	45.7 ± 22.9
≥ 10 years before PD	49 (13)	34.7 ± 21.8	45.4 ± 23.2
Geriatric Depression Scale score ≥ 7, yes	95 (20)	40.4 ± 24.4	51.9 ± 22.8
< 7	379 (80)	28.1 ± 21.6	40.1 ± 23.4

Hypnotic/anxiolytic/sedative use, never	351 (74)	28.9 ± 22.2	41.7 ± 23.6
past	41 (9)	37.3 ± 21.1	46.2 ± 25.3
current	79 (17)	34.0 ± 24.4	43.9 ± 23.7
Antidepressant use, never	299 (64)	29.0 ± 22.2	40.2 ± 23.8
past	47 (10)	33.9 ± 21.1	47.8 ± 25.0
current	125 (26)	32.8 ± 23.9	45.9 ± 22.6
Low social support	106 (22)	37.1 ± 23.2	42.8 ± 21.0
high	371 (78)	28.7 ± 22.1	42.3 ± 24.5
Number of stressful life events, ≥ 3	211 (44)	36.7 ± 25.1	46.2 ± 24.4
< 3	264 (56)	25.7 ± 19.3	39.4 ± 22.9
Perception of Health Care, < 8	104 (22)	35.3 ± 24.9	43.3 ± 21.0
≥ 8	366 (78)	29.2 ± 21.8	42.3 ± 24.5

Table 4-2. Linear regressions of insomnia scores on neuropsychiatric measures, adjusted for gender, age, duration of Parkinson's disease in years, and UPDRS-III (motor signs severity). PEG Study 2019.

Neuropsychiatric measures	Insomnia					
	Total (N=477)		Women (N= 183)		Men (N= 294)	
	N	MD (95% CI)	N	MD (95% CI)	N	MD (95% CI)
Ever depression diagnosis vs. Never	182/295	**7.47 (2.85, 12.09)**	71/112	**12.27 (4.91, 19.63)**	111/183	4.89 (-0.99, 10.76)
Ever depression diagnosis before 10 years of PD vs. Never	62/295	**10.36 (4.52, 16.20)**	31/112	**20.10 (11.41, 28.78)**	31/183	2.05 (-4.74, 8.85)
Ever depression diagnosis less than 10 years of PD vs. Never	117/295	5.34 (-0.01, 10.68)	38/112	6.46 (-2.61, 15.52)	79/183	4.98 (-1.57, 11.53)
Ever use - any antidepressant vs. Never	172/299	2.81 (-1.46, 7.07)	70/111	1.54 (-5.62, 8.70)	102/188	3.67 (-1.68, 9.02)
Ever anxiety diagnosis vs. Never	158/319	**7.62 (2.83, 12.42)**	68/115	**7.70 (0.28, 15.13)**	90/204	**7.60 (1.37, 13.83)**
Ever anxiety diagnosis before 10 years of PD vs. Never	49/319	**7.20 (0.79, 13.61)**	27/115	**11.39 (1.3, 21.48)**	22/204	2.38 (-4.28, 9.05)
Ever anxiety diagnosis less than 10 years of PD vs. Never	109/319	**9.04 (3.47, 14.61)**	41/115	6.86 (-2.06, 15.78)	68/204	**10.21 (3.09, 17.33)**
Ever use - hypnotic/sedative/anxiolytic vs. Never	120/351	**6.14 (1.52, 10.76)**	42/139	**8.37 (0.47, 16.27)**	78/212	4.86 (-0.80, 10.53)
Ever depression and/or anxiety diagnosis vs. Never	229/248	**6.68 (2.47, 10.88)**	93/90	6.61 (-0.27, 13.49)	136/158	**6.83 (1.5, 12.17)**
Ever depression/anxiety diagnosis before 10 years of PD vs. Never	79/248	**8.74 (3.52, 13.95)**	42/90	**13.75 (5.50, 22.01)**	37/158	4.16 (-1.98, 10.3)

Ever depression/anxiety diagnosis less than 10 years of PD vs. Never	148/248	**5.64 (0.67, 10.61)**	50/90	0.98 (-7.31, 9.26)	98/158	**7.96 (1.75, 14.17)**
Ever use - antidepressant and/or hypnotic/sedative/anxiolytic vs. Never	219/258	**3.84 (-1.9, 9.58)**	84/99	8.18 (-1.61, 17.96)	135/159	1.13 (-5.87, 8.13)
Ever depression and/or anxiety diagnosis and/or medication vs. Never	265/212	**6.95 (2.74, 11.15)**	107/76	3.73 (-3.28, 10.74)	158/136	**8.81 (3.6, 14.03)**
Current use - Any antidepressant vs. No current use	125/346	1.97 (-2.55 , 6.49)	52/129	-1.86 (-9.04 , 5.33)	73/217	4.52 (-1.28 , 10.33)
Selective serotonin reuptake inhibitors vs. No	92/379	2.83 (-2.19 , 7.84)	32/149	-0.24 (-8.69 , 8.22)	60/230	4.53 (-1.69 , 10.75)
Non-selective monoamine reuptake inhibitors vs. No	7/464	-3.77 (-20.28 , 12.74)	6/175	0.64 (-17.31 , 18.59)	1/289	
Other antidepressants vs. no	36/435	1.16 (-6.34 , 8.66)	19/162	-0.81 (-11.37 , 9.75)	17/273	3.25 (-7.49 , 13.99)
Current use - Any anxiolytic, hypnotic, sedative vs. No current use	79/392	3.33 (-1.99 , 8.66)	26/155	-1.06 (-10.21 , 8.08)	53/237	5.59 (-0.96 , 12.13)
Benzodiazepine derivatives vs. No	64/407	1.55 (-4.28 , 7.39)	19/162	-5.13 (-15.6 , 5.34)	45/254	4.54 (-2.47 , 11.55)
Other hypnotics, sedatives, anxiolytics vs. No	23/448	2.47 (-6.74 , 11.67)	8/173	4.88 (-10.75 , 20.52)	15/275	1.08 (-10.34 , 12.51)
Low social support vs. high	106/371	**8.56 (3.84, 13.27)**	50/133	**11.03 (4.04,18.01)**	56/238	**6.80 (0.40, 13.21)**
Stressful life events, more than 3 vs. less than 3	211/264	**8.96 (4.9, 13.02)**	91/91	4.5 (-2.01, 11.02)	120/173	**11.99 (6.81, 17.16)**

Perception of health care quality, below 8 vs. above 8	104/366	**5.53 (0.76, 10.3)**	40/139	7.29 (-0.38, 14.96)	64/227	4.54 (-1.57, 10.65)

MD= Mean differences in MOS-Sleep standardized scores, adjusted for sex, age, PD duration, and UPDRS-III (motor signs severity). Not adjusted for gender in stratified models.

Table 4-3. Linear regressions of EDS scores on neuropsychiatric measures, adjusted for gender, age, duration of Parkinson's disease in years, and UPDRS-III (motor signs severity). PEG Study 2019.

Neuropsychiatric measures	EDS		
	Total (N=477)	**Women (N=183)**	**Men (N=294)**
	MD (95% CI)	MD (95% CI)	MD (95% CI)
Ever depression vs. Never	**8.40 (3.68, 13.13)**	**7.04 (0.15, 13.94)**	**9.39 (3.08, 15.70)**
Ever depression before 10 years vs. Never	**11.30 (4.77, 17.70)**	**13.43 (3.01, 23.84)**	**9.78 (1.84, 17.71)**
Ever depression less than 10 years PD vs. Never	**8.01 (2.41, 13.60)**	3.03 (-4.04, 10.1)	**10.61 (3.06, 18.16)**
Ever antidepressant medication vs. Never	**6.17 (1.80, 10.50)**	6.76 (-0.16, 13.69)	**6.00 (0.43, 11.57)**
Ever anxiety vs. Never	3.97 (-0.79, 8.72)	0.44 (-6.41, 7.29)	6.13 (-0.34, 12.60)
Ever anxiety before 10 years vs. Never	6.11 (-0.94, 13.20)	4.12 (-5.76, 14.01)	8.49 (-1.37, 18.34)
Ever anxiety less than 10 years PD vs. Never	4.15 (-1.11, 9.41)	0.03 (-7.59, 7.64)	6.48 (-0.58, 13.54)
Ever hypnotic/sedative/anxiolytic medication vs. Never	2.81 (-2.11, 7.74)	4.41 (-4.09, 12.91)	2.01 (-4.00, 8.01)
Ever depression and/or anxiety vs. Never	**7.24 (2.69, 11.8)**	4.70 (-1.87, 11.27)	**8.87 (2.73, 15.02)**
Ever depression/anxiety before 10 years vs. Never	**8.25 (2.32, 14.2)**	8.79 (-0.18, 17.75)	**8.00 (0.24, 15.75)**
Ever depression/anxiety less than 10 years PD vs. Never	**6.58 (1.44, 11.7)**	1.46 (-5.39, 8.31)	**9.35 (2.41, 16.3)**
Ever antidepressant and/or anxiety medication vs. Never	3.39 (-2.91, 9.69)	7.87 (-2.91, 18.65)	0.65 (-6.96, 8.27)
Ever depression and/or anxiety and/or medication vs. Never	**8.09 (3.55, 12.6)**	5.83 (-1.00, 12.67)	**9.49 (3.54, 15.43)**
Current use any antidepressant vs. No current use	4.66 (-0.10 , 9.41)	-0.30 (-7.57 , 6.96)	**8.06 (1.81 , 14.31)**
Selective serotonin reuptake inhibitors vs. No	5.44 (0.16 , 10.72)	-1.83 (-10.37 , 6.7)	**9.45 (2.77 , 16.14)**

Non-selective monoamine reuptake inhibitors vs. No	-11.89 (-29.3 , 5.52)	-5.46 (-23.56 , 12.65)	-47.9 (-94.48 , -1.33)
Other antidepressants vs. no	5.49 (-2.42 , 13.4)	1.97 (-8.68 , 12.63)	9.52 (-2.09 , 21.12)
Current use - Any anxiolytic, hypnotic, sedative vs. No current use	0.53 (-5.11 , 6.16)	0.02 (-9.21 , 9.26)	0.83 (-6.30 , 7.96)
Benzodiazepine derivatives vs. No	0.92 (-5.25 , 7.08)	-6.64 (-17.20 , 3.91)	4.33 (-3.27 , 11.94)
Other hypnotics, sedatives, anxiolytics vs. No	1.66 (-8.07 , 11.39)	12.62 (-3.08 , 28.31)	-3.94 (-16.33 , 8.44)
Low social support vs. high	1.75 (-3.29, 6.79)	2.89 (-4.33, 10.11)	0.72 (-6.26, 7.70)
Stressful life events, more than 3 vs. less than 3	**6.72 (2.39, 11.04)**	5.12 (-1.44, 11.69)	**7.71 (1.98, 13.44)**
Perception of health care quality, below 8 vs. above 8	0.80 (-4.25, 5.86)	-4.41 (-12.28, 3.46)	3.85 (-2.73, 10.42)

MD= Mean differences in MOS-Sleep standardized scores, adjusted for gender, age, PD duration, UPDRS-III (motor signs severity). Not adjusted for gender in stratified models.

Table 4-4. Linear mixed models: association of PD-related characteristics and change in sleep problems scores across two points (n=156 with two sleep measurements). PEG Study 2019.

Fixed effects	β coefficient[a] (95% CI)
Outcome: Insomnia	
Intercept	40.34 (26.06, 54.62)
Follow-up time	-1.93 (-4.19, 0.33)
GDS ≥ 7	**11.61 (6.73, 16.48)**
GDS ≥ 7 * time	0.12 (-4.68, 4.92)
Outcome: EDS	
Intercept	33.41 (18.56, 48.26)
Follow-up time	1.59 (-0.72, 3.91)
GDS ≥ 7	**7.84 (2.71, 12.96)**
GDS ≥ 7 * time	-1.01 (-5.87, 3.85)

a- Adjusted for gender, and time-varying: age, PD duration, UPDRS-III, and LED (levodopa only)

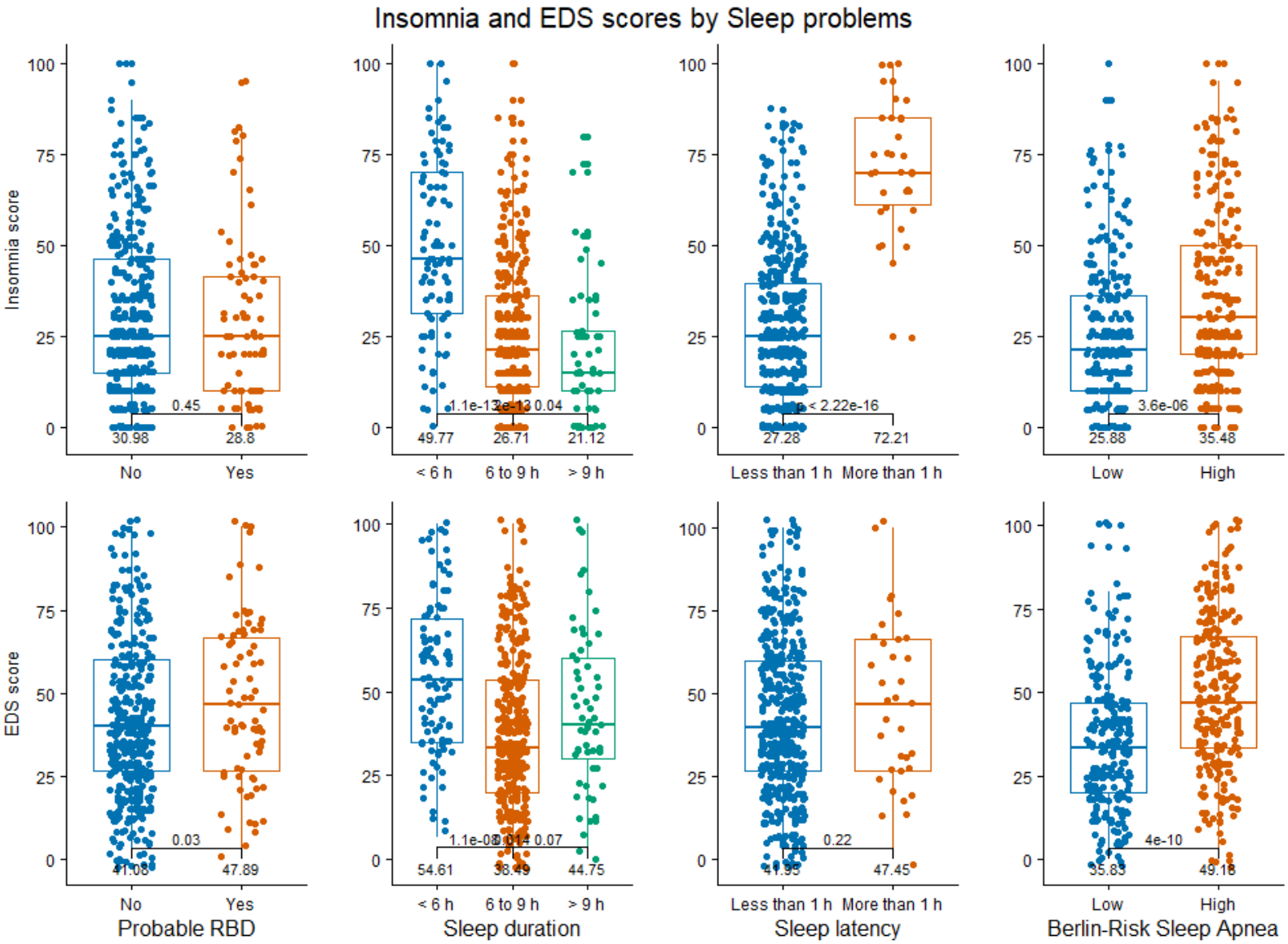


Figure 4-1. Insomnia and EDS mean scores by other sleep characteristics. RBD= REM Sleep Behavior disorder. PEG Study 2019.

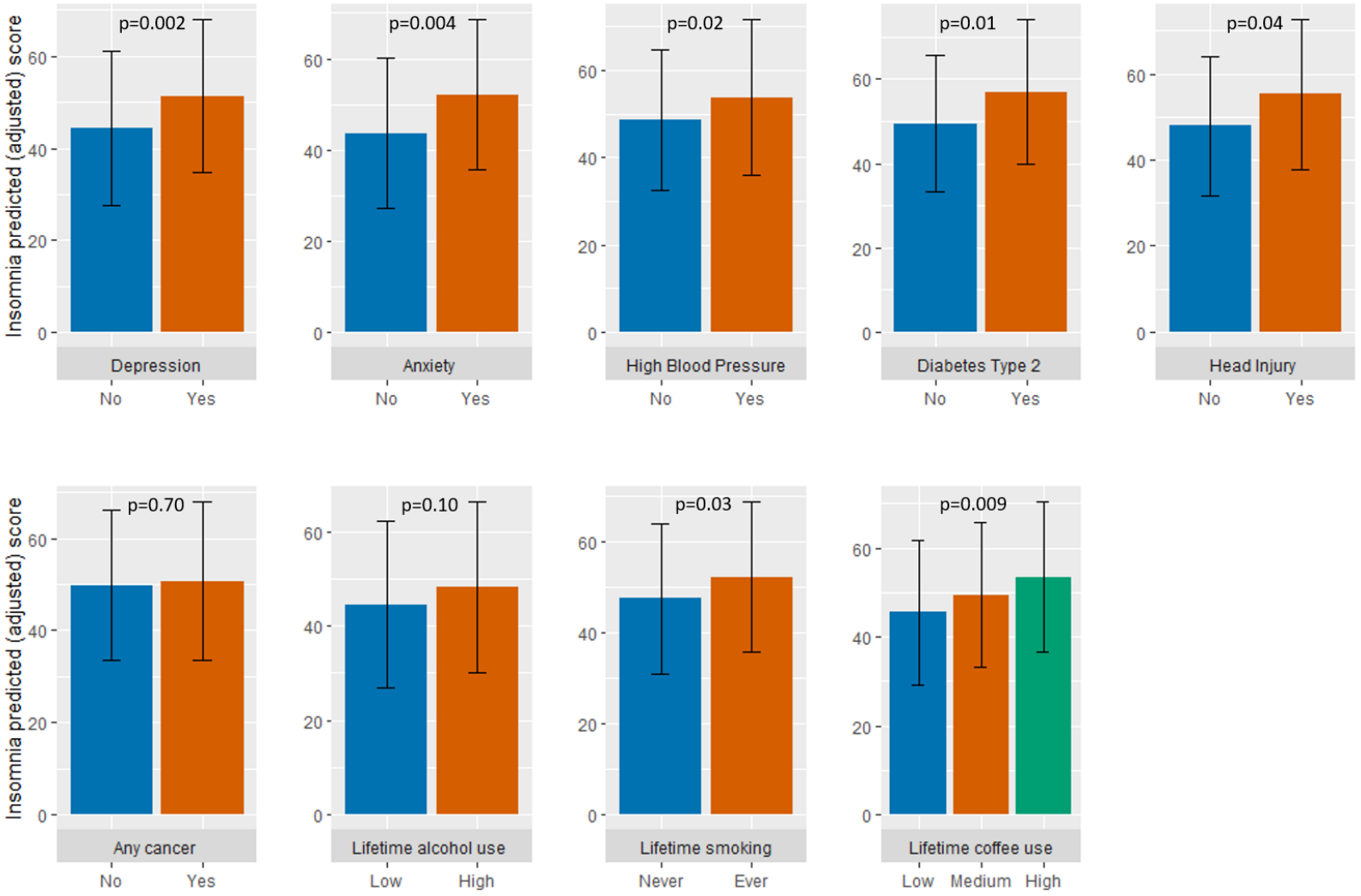


Figure 4-2. Insomnia predicted mean scores by co-morbidities and lifestyle characteristics, adjusted for age, PD duration, gender and ethnicity. PEG Study 2019.

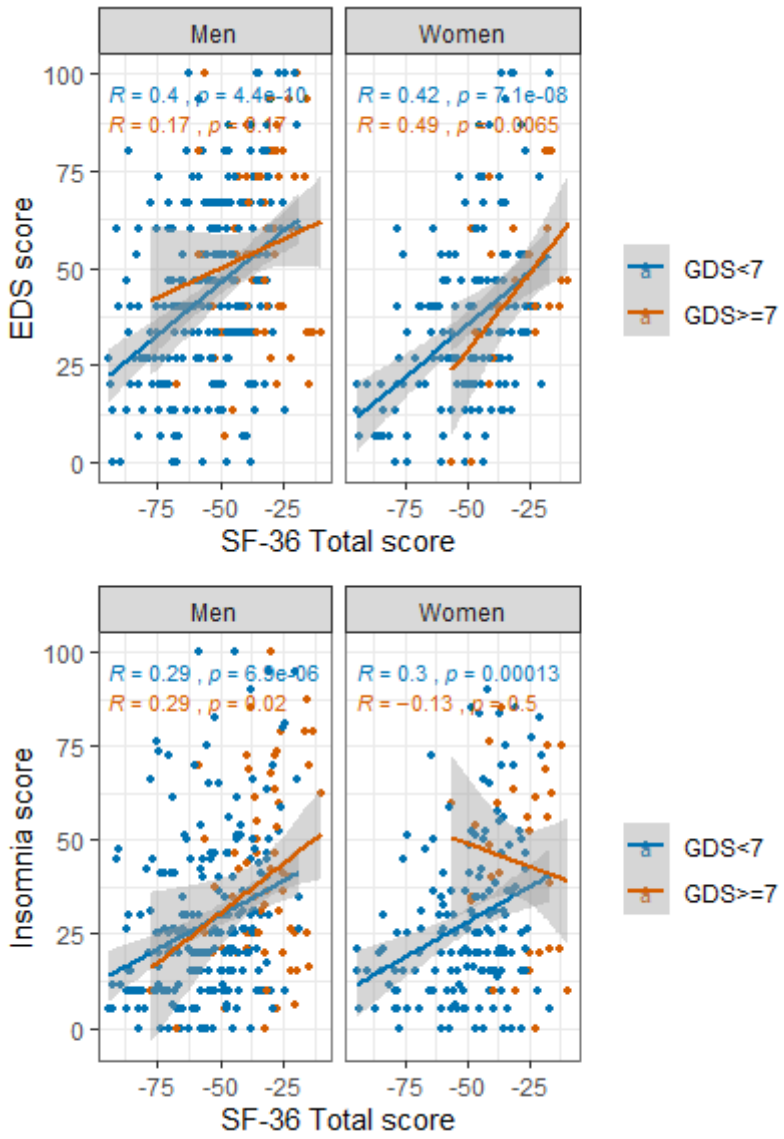


Figure 4-3. Scatterplot of sleep scores by health-related quality of life measured by SF-36 scores, stratified by Geriatric Depression Scale (GDS) <7 and 7+. SF-36 scores are shown multiplied by (-1), where larger scores represent worse quality of life. Including best fit linear correlation line and Pearson correlation coefficients and p-values. PEG Study 2019.

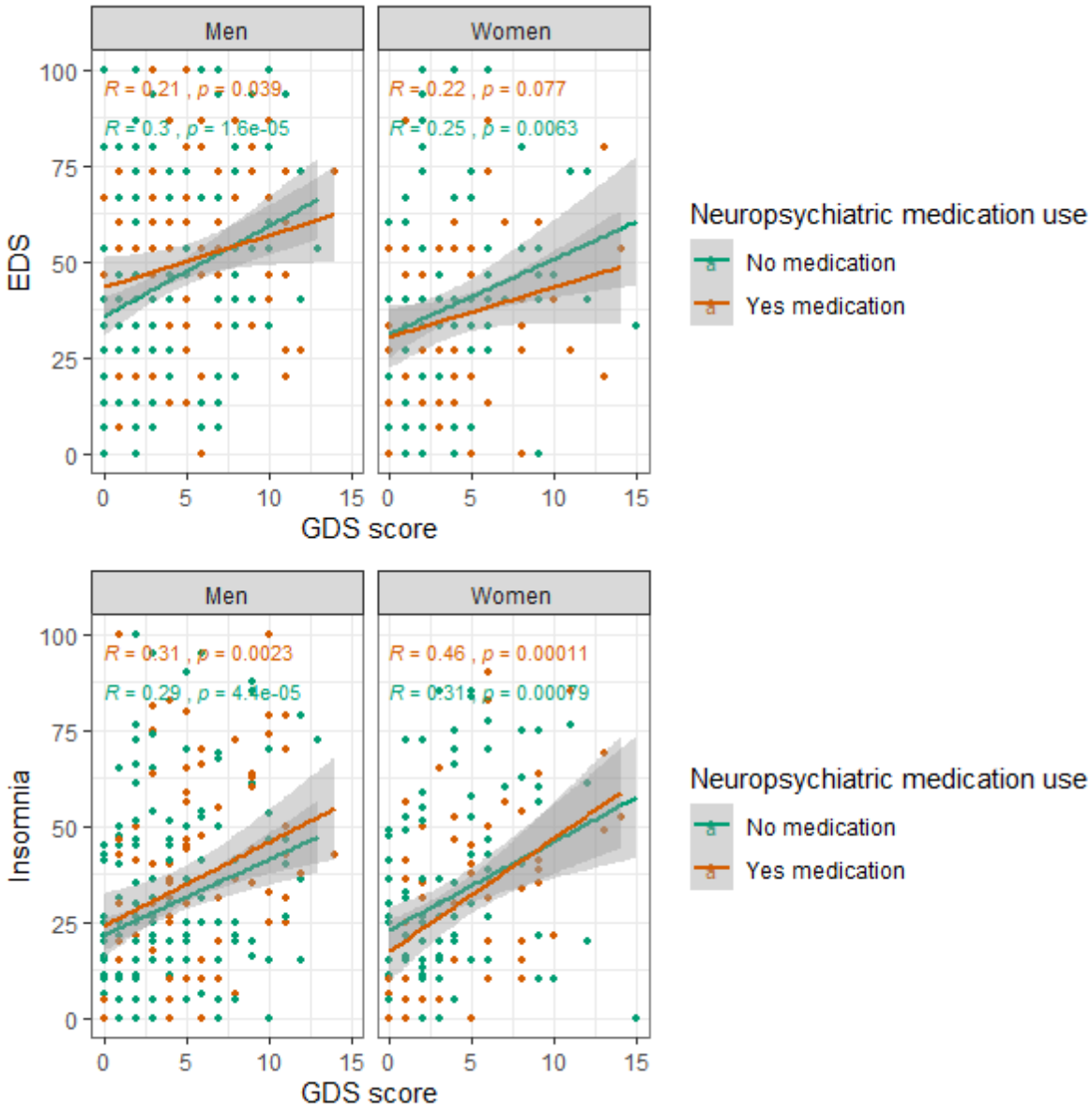


Figure 4-4. Scatterplot of sleep scores by Geriatric Depression Scale (GDS) stratified by concurrent medication use and gender. Including best fit linear correlation line and Pearson correlation coefficients and p-values. PEG Study 2019.

Table S4-1. Linear mixed models: association of depression symptoms (GDS) and change in sleep problems scores across two points on average 2.2 years apart (n=156 with two sleep measurements). Sensitivity analysis with different GDS cut-offs, and adjustment variables. PEG Study 2019.

	Insomnia		**EDS**	
	Model 1	**Model 2**	**Model 1**	**Model 2**
	β coefficient[1] (95% CI)	**β coefficient[2] (95% CI)**	**β coefficient[1] (95% CI)**	**β coefficient[2] (95% CI)**
Intercept	42.87 (29.22 , 56.53)	38.92 (24.92 , 52.92)	39.34 (24.73 , 53.96)	32.5 (17.74 , 47.26)
Follow-up time	-0.85 (-3.18 , 1.49)	-1.16 (-3.54 , 1.23)	2.41 (-0.07 , 4.88)	2.02 (-0.47 , 4.5)
GDS ≥ 5	**14.22 (10.32 , 18.11)**	**14.12 (10.04 , 18.2)**	**10.09 (5.89 , 14.3)**	**9.04 (4.69 , 13.38)**
GDS ≥ 5 * time	-1.12 (-5.18 , 2.94)	-1.19 (-5.3 , 2.92)	-1.31 (-5.57 , 2.96)	-1.27 (-5.52 , 2.97)
Intercept	44.15 (30.23 , 58.08)	40.34 (26.06 , 54.62)	39.93 (25.23 , 54.63)	33.41 (18.56 , 48.26)
Follow-up time	-1.54 (-3.74 , 0.67)	-1.93 (-4.19 , 0.33)	2.05 (-0.26 , 4.37)	1.59 (-0.72 , 3.91)
GDS ≥ 7	**12.23 (7.54 , 16.92)**	**11.61 (6.73 , 16.48)**	**10.15 (5.17 , 15.13)**	**7.84 (2.71 , 12.96)**
GDS ≥ 7 * time	0.13 (-4.56 , 4.83)	0.12 (-4.68 , 4.92)	-1.28 (-6.16 , 3.61)	-1.01 (-5.87 , 3.85)
Intercept	44.62 (30.55 , 58.68)	40.37 (25.99 , 54.76)	40.73 (25.9 , 55.56)	33.53 (18.62 , 48.43)
Follow-up time	-1.57 (-3.67 , 0.54)	-2.01 (-4.16 , 0.15)	1.74 (-0.45 , 3.93)	1.33 (-0.86 , 3.51)
GDS ≥ 10	**15.64 (8.67 , 22.6)**	**15.54 (8.45 , 22.62)**	**10.27 (2.85 , 17.68)**	**9.69 (2.23 , 17.14)**
GDS ≥ 10 * time	-1.46 (-7.71 , 4.8)	-1.66 (-8.07 , 4.75)	-1.06 (-7.47 , 5.35)	-1.13 (-7.49 , 5.22)

GDS=Geriatric Depression Scale

1- Adjusted for gender, and time-varying: age, PD duration

2- Adjusted for gender, and time-varying: age, PD duration, and UPDRS-III, and LED (levodopa only)

5 Public Health Relevance and Expected Contributions

This dissertation analyzes the contribution of multiple clinical factors, related and not related to PD, as potential causes and effects of self-reported sleep problems in PD patients from a population-based cohort. We found that RBD features in adult life were associated with faster cognitive decline, while faster progression of motor dysfunction was associated with pRBD only amongst those who exhibited a PIGD motor subtype at baseline. In addition, we found that patients with longer PD duration, higher LED, worse non-motor and autonomic symptoms have worse EDS and insomnia symptoms, at an average of six years since first PD diagnosis, with motor symptoms (particularly tremor and motor fluctuations) being specifically related to increased insomnia, and not EDS. Finally, we show that history of depression and anxiety diagnoses also predict prevalent symptoms of insomnia and EDS at the same six years of average PD duration, with differences in men and women in relation to characteristics of mood disorders and their associations with sleep.

Sleep disorders are highly prevalent in the older adult population and constitute a public health problem that impact quality of life on the individual level, as well as families' and communities' well-being (Garbarino, Lanteri, Durando, Magnavita, & Sannita, 2016; Mattis & Sehgal, 2016). The increase in the proportion of older adults in the total population (i.e., population aging) is a process occurring in all countries of the world, at different rates and patterns (United Nations, 2015). This process is projected to impact nearly all sectors of society, including public health (He, Goodkind, & Kowal, 2016). In this context, diseases which have their prevalence and

incidence associated with aging, such as Parkinson's disease, are projected to represent an increasing burden on health services and systems.

In this context, it is of public health relevance to study sleep disorders in PD using population-based and longitudinal study designs (Videnovic & Högl, 2015). Characterizing these problems, their risk factors and role in disease progression, in light of modern epidemiological methods, may contribute to the knowledge in the field of neurodegenerative disorders and to the design of more effective intervention strategies to improve patients' quality of life.

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