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SLEEP (M. THORPY AND M. BILLIARD, SECTION EDITORS)

Polysomnographic Predictors of Sleep, Motor, and Cognitive Dysfunction Progression in Parkinson's Disease

Femke Dijkstra[1,2,3] · **Ilse de Volder**[1,2,4,5] · **Mineke Viaene**[3] · **Patrick Cras**[1,2,6] · **David Crosiers**[1,2,6]

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Abstract

Purpose of Review Sleep disturbances are an important nonmotor feature of Parkinson's disease (PD) that can cause polysomnographic (PSG) alterations. These alterations are already present in early PD and may be associated with a specific disease course. This systematic review describes the role of PSG variables as predictors of sleep dysfunction, motor and cognitive dysfunction progression in PD.

Recent Findings Nineteen longitudinal cohort studies were included. Their main findings were that (1) REM sleep behavioral events, REM sleep without atonia (RSWA), and electroencephalography (EEG) changes (mainly microsleep instability) are predictors of the development of REM sleep behavior disorder (RBD); (2) RBD, RSWA, and lower slow-wave sleep energy predict motor progression; (3) RBD, EEG slowing, and sleep spindles changes are predictors of cognitive deterioration; and (4) OSA is associated with severe motor and cognitive symptoms at baseline, with inconsistent findings on the effect of continuous positive airway pressure (CPAP) therapy for these symptoms.

Summary The results of our systematic review support a role of the video-PSG in disease progression prediction in PD and its usefulness as a biomarker. However, future studies are needed to investigate whether treatment of these PSG abnormalities and sleep disturbances may have a neuroprotective effect on disease progression.

Keywords Parkinson's disease · Polysomnography · Sleep dysfunction · Motor progression · Cognitive dysfunction

Introduction

Background

Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases that affects over 6 million people worldwide [1]. Although PD is regarded as a classical movement disorder, patients also suffer from a spectrum of nonmotor symptoms, such as autonomic dysfunction, psychiatric symptoms, and cognitive deterioration [2]. Sleep dysfunction is another important nonmotor feature that can cause alterations on a video-polysomnography (PSG). The most famous and investigated example is the rapid-eye-movement (REM) sleep behavior disorder (RBD), a REM sleep parasomnia characterized by persistent muscle tonus during REM sleep (REM sleep without atonia [RSWA]), and dream-enacting behavior [3]. However, previous research suggests that the sleep-related PD spectrum is much broader than RBD. A recent large meta-analysis that compared PSGs of patients with PD with healthy controls found a reduction in total sleep time, REM sleep percentage, slow-wave sleep

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✉ Femke Dijkstra
Femke.Dijkstra@uza.be

1 Department of Neurology, Antwerp University Hospital, Drie Eikenstraat 655, 2650 Edegem, Belgium

2 Faculty of Medicine and Health Sciences, Translational Neurosciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

3 Laboratory for Sleep Disorders and Department of Neurology, St.-Dimpna Regional Hospital, J.-B. Stessensstraat 2, 2440 Geel, Belgium

4 Department of Psychiatry, Antwerp University Hospital, Drie Eikenstraat 655, 2650 Edegem, Belgium

5 Multidisciplinary Sleep Disorders Center, Antwerp University Hospital, Drie Eikenstraat 655, 2650 Edegem, Belgium

6 Born-Bunge Institute, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

percentage and sleep efficiency, and a higher apnea–hypopnea index (AHI) and periodic limb movement during sleep (PLMS) index in PD patients [4•]. Furthermore, electroencephalogram (EEG) abnormalities (spectral changes, sleep spindles abnormalities) [5–8], lower REM density [9], lower heart rate variability [10–12], and supine body position [13–15] during sleep have been described in PD.

The example of RBD, which is regarded as a specific prodromal PD symptom and can be present 10–20 years before PD diagnosis [16], suggests that sleep disturbances and PSG alterations often precede motor and cognitive deterioration in PD. Sleep disturbance is also suggested to be a risk and progression factor in PD [17•]. However, whether these PSG alterations are also associated with development of specific PD symptoms or influence disease progression in PD is less clear. This systematic review investigates whether PSG variables predict sleep dysfunction, motor progression, and cognitive deterioration in PD. This may give more insight in the relation between the neurophysiology of sleep dysfunction, other PD symptoms, and disease course in PD. Furthermore, it may underline the clinical relevance of the video-PSG as a biomarker for disease progression prediction in PD and sleep as a possible therapeutic target in PD.

The Video-Polysomnography

In sleep medicine, the widely used instrument to determine the neurophysiologic correlates of sleep and sleep disorders is the video-PSG (Fig. 1). The video-PSG consists of several channels for an electro-oculogram (EOG), electro-myogram (EMG), and EEG. These channels are used to measure sleep stages and abnormalities in cerebral activity and muscle activity during sleep. Furthermore, several respiratory variables are recorded to evaluate sleep-related breathing disorders, with nasal airflow channels, respiratory effort channels, oximetry channels, and snoring detector channels. Finally, a video-PSG includes an electrocardiography channel, a pulse transit time channel, a position detector, a light detector, and a video to record abnormal movements and behavior during sleep. With all these variables combined, a video-PSG comprehensively evaluates all physiological aspects of sleep and sleep dysfunction.

A video-PSG is traditionally analyzed visually for macro-architecture, movements during sleep and sleep-related breathing events, according to standardized criteria from the American Academy of Sleep Medicine (AASM) [18]. Although time-consuming, this is currently the gold standard for clinical practice. Novel techniques are being developed for automated PSG scoring and more comprehensive methods are being developed for PSG data analysis [19]. These methods, for example, focus on sleep micro-architecture analysis, EEG and EMG quantification, and machine learning algorithms that combine different PSG variables. Most of them, however, are currently only used for research purposes.

Method

Search Strategy

We searched Medline, Web of Science, and the Cochrane library between 26/05/2022 and 01/06/2022 with the terms "Parkinson's disease" and "polysomnography." Our complete search strategies for the databases are available in S1-3. References of all included articles were searched as well. Abstracts were screened for eligibility. Studies with a longitudinal design were included, that investigated:

- Patients with a clinical diagnosis of PD as *study population* (not patients with PD versus healthy controls or patients with PD in the prediagnostic stage).
- Polysomnographic variables as *independent variables.*
- Sleep dysfunction progression, (2) motor progression, and (3) cognitive deterioration or a combination as *outcome variables.*

Only original research papers were included. Papers written in English or Dutch were included. Papers that investigated a specific intervention with sleep dysfunction as an outcome variable (such as the impact of deep brain stimulation on sleep dysfunction, treatment with Melatonin, etc.) were excluded, except for continuous positive airway pressure (CPAP) therapy. If similar variables from the same cohort were published in different reports, we included the study with the longest follow-up design. The number of records identified was recorded in a PRISMA flow chart [20] (Fig. 2). We used the Newcastle–Ottawa Quality (NOS) assessment scale for cohort studies for quality assessment [21]. According to the NOS score standard, cohort studies could be classified as low-quality (scores of 0–4), moderate-quality (scores of 5–6), and high-quality (scores ≥ 7).

Results

Search Results

The search strategy resulted in 1577 reports. After removing duplicates and screening the title and abstracts, 19 studies that fulfilled the inclusion criteria were selected (Fig. 2). Their results are summarized in Table 1 and the NOS quality assessment results are available in table S4. Seventy-nine percent of the studies had a NOS score ≥ 7 (high-quality).

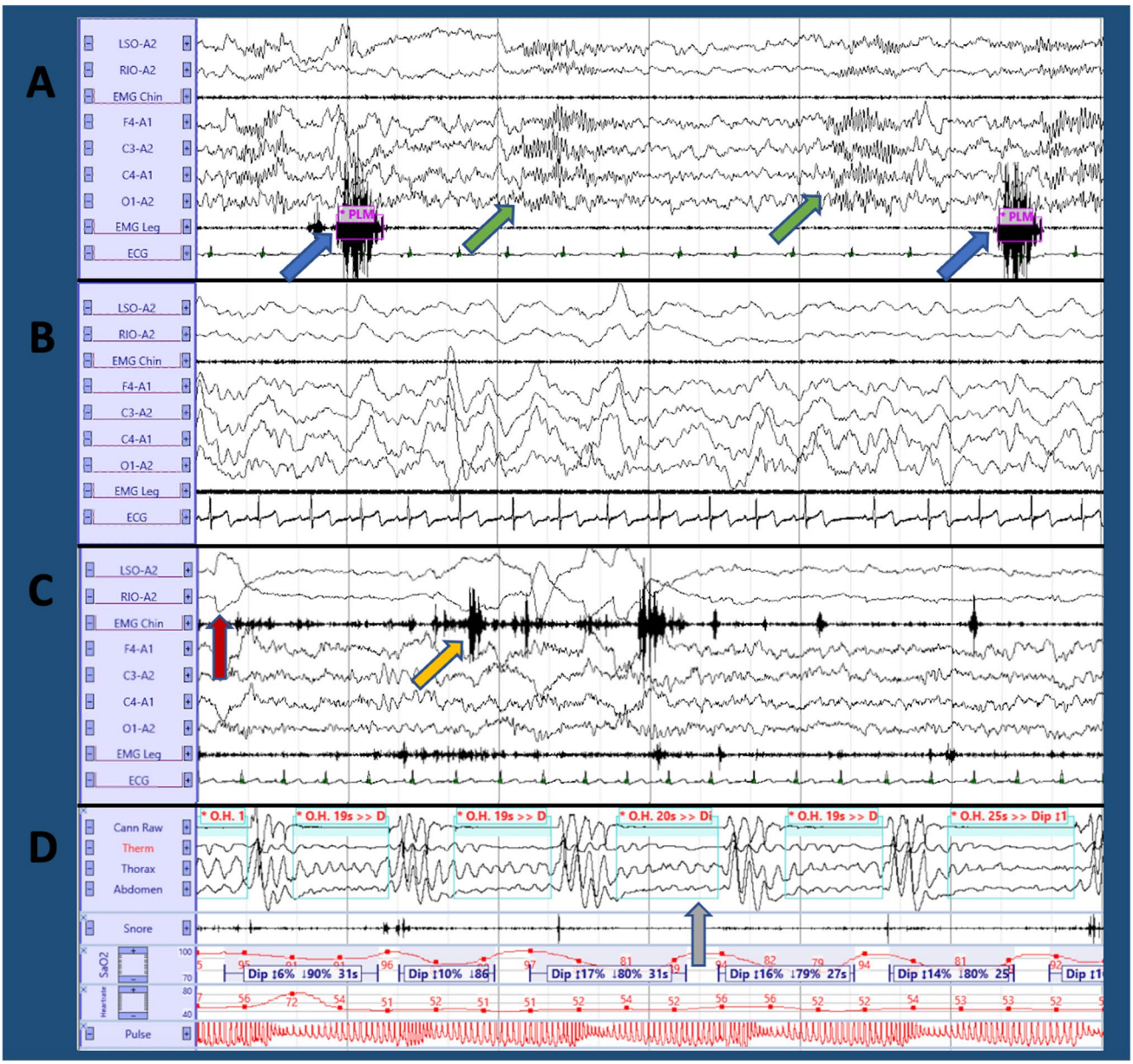

Fig. 1 The video-polysomnography. A polysomnograpic 18-s epoch with 2 electro-oculography (EOG) channels (LSO-A2 and RIO-A2), 4 electroencephalography (EEG) channels, an elecrocardiography (ECG) channel, a chin electromyography (EMG) channel, and a leg EMG channel (covering both tibialis anterior muscles). **A** NREM sleep stage 2 with sleep spindles, K complexes and periodic limb movement. **B** NREM sleep stage 3 with slow wave sleep. **C** Rapid-eye-movement (REM) sleep with REM sleep without atonia (RSWA). **D** A 3-min epoch with respiratory-related variables: a snoring detector channel, a pulse transit time channel, a peripheral pulse oximetry channel, nasal airflow channels, and 2 respiratory effort channels on thorax and abdomen. Several obstructive hypopneas are shown. *Blue arrows:* periodic limb movements. *Green arrows:* sleep spindles. *Red arrow:* rapid-eye-movements on the ocular channels. *Yellow arrow:* RSWA on the chin EMG channel. *Grey arrow:* obstructive hypopnea

REM Sleep Variables

Ten studies have investigated the predictive value of REM sleep-related variables in disease progression prediction in PD [22–31]. Most studies focused on RBD. Zimansky and coworkers investigated *sleep dysfunction* as the outcome variable, in a cohort of 158 de novo PD patients with 6 years of follow-up and PSG data both at baseline and follow-up [22]. They showed that the prevalence of RBD increased from 24 to 52%. PSG predictors for the development of RBD were REM sleep behavioral events (RBE, motor events without a sufficient amount of RSWA) and RSWA (the persistent muscle tonus during REM sleep without dream-enacting behavior). RSWA severity also increased during the follow-up

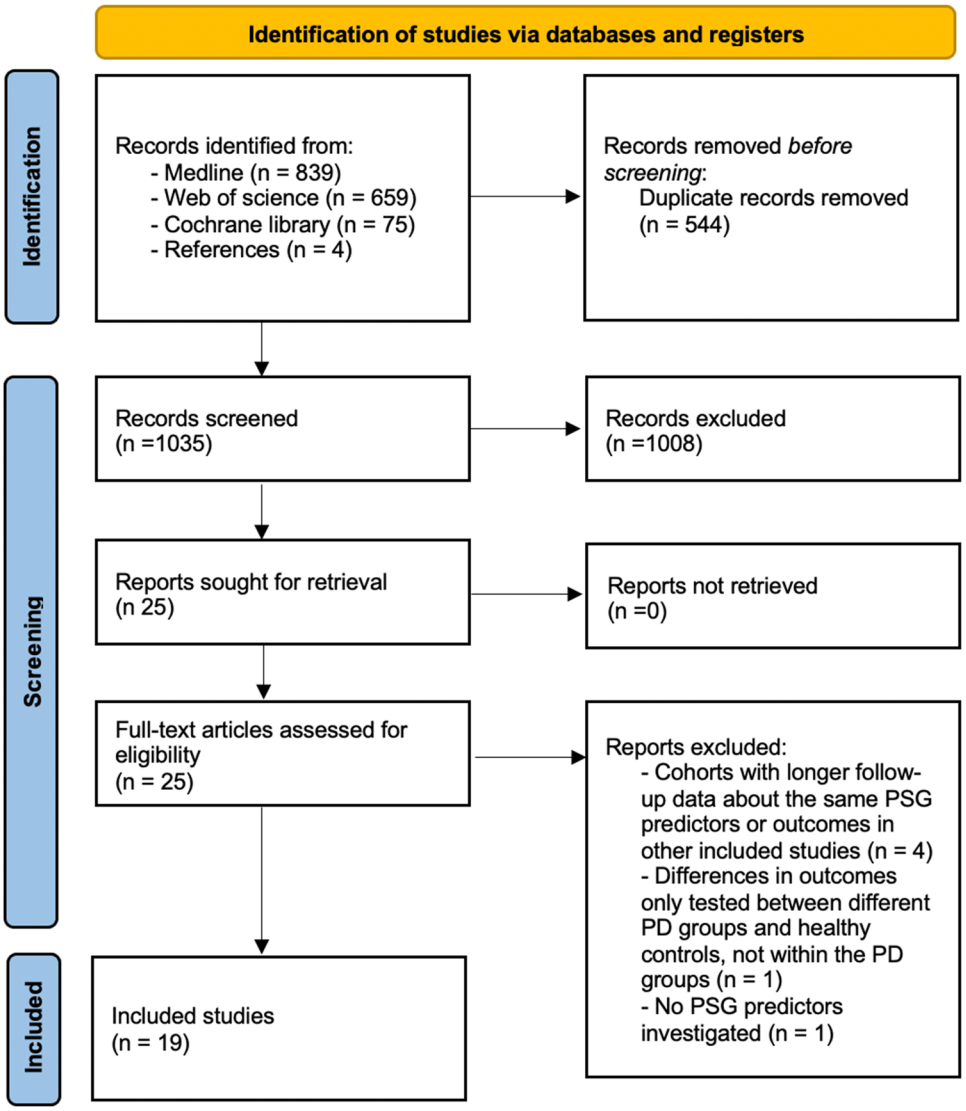

Fig. 2 The PRISMA flowchart. The results of the search strategy are summarized in the PRISMA flow diagram

period. These results were confirmed in other cohorts: Nomura and coworkers also reported RSWA as predictor of the development of RBD, in a cohort of 82 PD patients with a follow-up period of 21 months [23]. Figorilli and coworkers investigated a cohort of 22 patients with PD and RBD at baseline and 3 years of follow-up and confirmed an increase in RSWA severity during the follow up period [24]. RBD severity remained stable in most patients. Bugalho and coworkers investigated predictors of other sleep-related symptoms and showed that RBD at baseline is a predictor of excessive daytime sleepiness (measured by SCOPA-SLEEP [32]) and both RBD and RSWA are predictors of disturbed nighttime sleep (measured by SCOPA-SLEEP) during follow-up [25].

The results of RBD as a predictor of *motor progression* in PD are inconsistent. For example, Sommerauer and coworkers investigated 59 PD patients (15 with RBD, 22 with RSWA, and 22 with normal REM sleep) and reported both RBD and RSWA as predictors of the Unified Parkinson Disease Rating Scale (UPDRS)-3 [33] increment over a period of 2.5 years of follow-up [27]. However, Mollenhauer and coworkers [26] and Bugalho and coworkers [25], however, found no effect of RBD at baseline on the UPDRS-3 score during follow-up.

The relation between RBD and *cognitive deterioration* has been investigated in several studies. Anang and coworkers [29] described a cohort of 80 PD patients with a mean follow-up of 4.4 years. They found that 34% of the patients developed dementia. RBD at baseline was a significant predictor for the development of dementia with an odds ratio of 49.7. The patients who converted also had higher RSWA severity at baseline. These results were validated in a larger cohort of 135 patients, with a follow-up of 4.2 years and a dementia conversion percentage of 22%. An odds ratio of 5.4 was found [30]. In a subgroup of this cohort, RSWA without DEB was no significant predictor of dementia conversion

Table 1 Summary of the included study results

Study	Outcome	Sample size (number)	Age (Y)	Gender (M %)	Disease duration (Y)	H&Y	BMI	PSG variables	Outcome variables	Follow up	Results
Zimansky 2021 [22] *	Sleep	Total 158 -31 RSWA analysis	60	65	–	–	–	RBD RBE RSWA	RBD RSWA	6 y	- RBD prevalence increased from 25 to 52% - RSWA severity increased in all subjects - RBD did not abate in individual subjects over time - Subjects with RBE at baseline phenoconverted into RBD
Nomura 2013 [23]**	Sleep Cognition	Total 82 -27 RBD -23 RSWA -32 normal REM	 77 72 75	 51 34 44	 8.8 5.1 7.0	 3.0 2.5 2.5	–	RBD RSWA	Development of dementia Development of RBD	21 m	- 12 subjects developed dementia - RBD predicts development of dementia (HR 14.1) - RSWA did not predict development of dementia - 26% of RSWA subjects developed RBD
Figorilli 2020 [24]	Sleep Motor Cognition	22	64	68	7.6	2	–	RBD RSWA	RBD RSWA NPE	3 y	- The course of RBD differed between subjects - RSWA severity increased in all subjects - RSWA severity correlated with executive dysfunction - Increase in RSWA correlated with motor complications severity

Table 1 (continued)

Study	Outcome	Sample size (number)	Age (Y)	Gender (M %)	Disease duration (Y)	H&Y	BMI	PSG variables	Outcome variables	Follow up	Results
Bugalho 2021 [25]	Sleep Motor Cognition	25	67	52	8.58	–	–	Total sleep time, RBD, RSWA, Motor event, PLMS, AHI, sleep stages, SE	SCOPA-sleep UPDRS 3 MoCA	4 y	- Lower N3 percentage was associated with MoCA decrease - Higher PLMS index and RBD were associated with SCOPA- daytime sleep increase - Higher RBD severity, motor events and tonic RSWA were associated with SCOPA-nighttime sleep increase - No significant associations between PSG data and UPDRS3 change
Mollenhauer 2019 [26]*	Motor Cognition	135	65	65	< 6 months diagnosis	–	27.6	RBD PLMS	UPDRS 3 MMSE	4 y	- Elevated PLMS index predicted cognitive decline, not motor progression - RBD did not predict cognitive decline
Sommerauer 2014 [27]	Motor	Total 59 -RBD 15 -RSWA 22 -Normal REM 22	 69 64 66	 54 54 53	 9.7 8.4 7.5	 2.4 2.4 2.2	–	RBD RSWA	UPRDS 3	2.5 y	- Both RBD and RSWA were predictors of UPDRS 3 increment
Bugalho 2021 [28]	Cognition	49	71	51	8.5	–	–	Total sleep time, RBD, RSWA, Motor event, PLMS, AHI, sleep stages	GDS (cognition)	3.4 y	- Significant interactions between RBD presence, tonic RSWA and GDS increase

Table 1 (continued)

Study	Outcome	Sample size (number)	Age (Y)	Gender (M %)	Disease duration (Y)	H&Y	BMI	PSG variables	Outcome variables	Follow up	Results
Anang 2014 [29]	Cognition	Total 80					–	RBD	Development of dementia		- RBD dramatically increased the risk of developing dementia (OR = 49.7, $p < 0.001$) - Mean % of tonic RSWA was higher in dementia converted participants (68% compared with 30.6%; OR 5 1.4 per 10%, p < 0.001) than in the nonconverted group
		Follow up: -PDD 27 -no PDD 53	71 64	81 54	6.0 5.4	2.8 2.3				4.7 y 4.2 y	- The % of phasic RSWA was higher in the dementia- converted group when compared with the nonconverted group (OR 5 1.3 per 10%, $p = 0.053$, not statistically different)
Anang 2017 [30] ** #	Cognition	135	–	–	–	-	–	RBD	Development of dementia	4.2 y	- RBD was a significant predictor of development of dementia (OR 5.4, $p < 0.001$)
Onofrj 2002 [31]	Sleep Cognition	80				1–4		RBD	Development of hallucinations Development of RBD	8 y	- RBD predicted development of hallucinations - RBD prevalence increased during follow-up

Table 1 (continued)

Study	Outcome	Sample size (number)	Age (Y)	Gender (M %)	Disease duration (Y)	H&Y	BMI	PSG variables	Outcome variables	Follow up	Results
Neikrug 2014 [36]***	Sleep	Total 38 - CPAP 19 - pCPAP 19 (3 weeks placebo, 3 weeks therapeutic CPAP)	67 68	63 74	–	1–3 1–3	27.8 27.2	CPAP therapy	Sleep stages Arousals PLMS TST SE AHI Time $Sa0_2 < 90\%$ MSLT	6 w	- CPAP therapy decreased NREM 2 and increased NREM 3 percentage - CPAP therapy decreased arousal index - CPAP therapy decreased AHI and time $Sa0_2 < 90\%$ - CPAP therapy decreased sleepiness measured by MSLT - No effect of CPAP on PLMS, TST or SE
Harmell 2016 [37] ***	Cognition	Total 86 -38 OSA -CPAP 19 -pCPAP 19	68 67 68	73 63 73	–	1–3 1–3 1–3	27.2 27.8 27.2	OSA CPAP therapy	NPE MMSE MoCA	6 m	- OSA was a significant predictor for MMSE and MoCA score - No significant difference in NPE scores between the treatment and placebo groups or within the treatment group
Meng 2020 [38]****	Motor	Total 67 -OSA—20 -OSA + CPAP + 26 -OSA + CPAP- 21	62 67 65	60 69 52	5.4 5.4 6.6	1.8 2.1 2.3	26.1 29.5 27.5	OSA CPAP therapy	Motor UPDRS TUG	1 y	- UPDRS3 was higher in OSA + compared to OSA—at baseline - No significant difference in motor progression between OSA- and OSA + CPAP- - UPDRS3 and TUG change was lower in OSA + CPAP + compared to OSAS + CPAP-

Table 1 (continued)

Study	Outcome	Sample size (number)	Age (Y)	Gender (M %)	Disease duration (Y)	H&Y	BMI	PSG variables	Outcome variables	Follow up	Results
Kaminska 2018 [39] ****	Sleep Cognition	Total 61 -OSA -: 19 -OSA CPAP + 21 -OSA CPAP—21	 61 66 66	 58 80 48	–	 1.8 2.1 2.3	 26.2 29.1 28.3	CPAP therapy RBD	MoCA PDSS ESS	1 y	- CPAP therapy improved MoCA score in subjects with an abnormal MoCA score at baseline - CPAP therapy improved PDSS score - No effect of CPAP on ESS score
Terzaghi 2017 [40]	Sleep Cognition	Total 36 -9 follow-up	72	–	9.9	–	26.7	CPAP therapy	ESS NPE AHI Sleep stages Arousal index PLMS index	3 m	- 75% drop out because of CPAP intolerance - No significant changes between baseline and follow-up were found on overall NPE scores, single cognitive domain areas, subjective sleepiness scales - Reduction in AHI (p 1⁄4 0.008) and a trend toward increase in NREM sleep stage 3 (p 1⁄4 0.063)

Table 1 (continued)

Study	Outcome	Sample size (number)	Age (Y)	Gender (M %)	Disease duration (Y)	H&Y	BMI	PSG variables	Outcome variables	Follow up	Results
Cesari 2021 [43]*	Sleep	Total 107 -normal REM 54 -RBE + 27 -RBD + 26	 62 63 64	 57 74 73	< 6 months diagnosis	–	–	Data driven model with 2 EEG and 2 EOG channels	Conversion DBE to RBD Conversion normal REM sleep to RBD	2 y	- A machine learning model, based mainly on micro-sleep instability and EEG spectral features, could identify RBD at baseline. The model could also predict development of RBD in subjects with RBE (AUC 0.87, sensitivity 77.78%, specificity 87.5%) - The same model could not predict development of RBD in subjects without RBE at baseline
Schreiner 2019 [44]	Motor	Total 129 -High SWE 65 -Low SWE 64	63 61 64	64 55 27	5.4 5.1 5.6	2.0 2.0 2.0	25.2 24.9 25.5	SWA SWE	UPDRS 3	4.6 y	- Subjects with high SWE had slower UPDRS 3 increments compared to subjects with low SWE - Higher SWE was strongly associated with slower progression of axial UPDRS 3 - SWE predicted progression of total UPDRS 3 score
Latreille 2016 [45]*****	Cognition	Total 68					–	EEG power spectral analyses (wake, NREM, REM)	Development of dementia	4.5 y	The best predictors for development of dementia: - REM slowing ratios posterior
		Follow up: -PDD 18 -no PDD 50	70 63	72 66	5.7 4.1	2.8 2.1					- Wake slowing ratios temporal and lower dominant occipital frequency

Table 1 (continued)

Study	Outcome	Sample size (number)	Age (Y)	Gender (M %)	Disease duration (Y)	H&Y	BMI	PSG variables	Outcome variables	Follow up	Results
Latreille 2015 [46]*****	Cognition	Total 68					–	NREM sleep spindles NREM slow waves	Development of dementia	4.5 y	- Lower spindle density in central, parietal and occipital regions was a significant predictor of development of dementia - Lower spindle amplitude in parietal and occipital regions was a significant predictor of development of dementia
		Follow up: -PDD 18 -no PDD 50	70 63 66	72	5.7 4.1	2.8 2.1					- Slow wave amplitude and density did not differ between groups

Y years, *M* male, *M* months, *H&Y* Hoehn and Yahr scale, *BMI* body mass index, *PSG* polysomnography, *RSWA* REM sleep without atonia, *RBD* REM sleep behavior disorder, *RBE* REM sleep behavioral event, *NPO* neuropsychological evaluation, *PLMS* periodic limb movement during sleep, *AHI* apnea/hypopnea index, *SE* sleep efficiency, *MoCA* Montreal Cognitive Assessment, *SCOPA* SCales for Outcomes in PArkinson's disease, *UPDRS* Unified Parkinson's Disease Rating Scale, *GDS* Global Deterioration Scale, *PDD* Parkinson disease dementia, *CPAP* continuous positive airway pressure, *TST* total sleep time, *MSLT* Multiple Sleep Latency Test, *OSA* obstructive sleep apnea, *TUG* Timed Up and Go test, *ESS* Epworth Sleepiness Scale, *EEG* electroencephalogram, *EOG* electro-oculogram, *AUC* area under the curve, *SWA* slow wave activity, *SWE* slow wave activity

* until *****: studies that investigated the same cohort of PD patients

#: 2 cohorts combined, in which 1 RBD was confirmed by PSG and 1 was diagnosed based on an expert interview

[23]. Other studies describe that RBD and RSWA at baseline can predict more subtle cognitive changes, such as the development of hallucinations [31] and an increase in (cognitive) global deterioration scale [28]. Mollenhauer and coworkers [26] and Bugalho and coworkers [25], however, found no effect of RBD at baseline on change in Mini-Mental State Examination (MMSE) [34] score or Montreal Cognition Assessment (MoCA) [35] score during follow-up.

OSA and Sleep-Related Breathing Variables

Five studies investigated the predictive value of OSA in disease progression prediction in PD, all of which are CPAP therapy trials [36–40]. Neikrug and coworkers [36] investigated the impact of CPAP therapy on *sleep dysfunction* in 38 patients with PD and OSA, with a randomized placebo-controlled cross-over design: 6 weeks of treatment or 3 weeks of placebo, followed by 3 weeks of therapeutic CPAP. Patients with therapeutic CPAP treatment showed a significant decrease in AHI, amount of time with $SaO_2 < 90\%$, NREM stage 2% and arousal index, with a significant increase in NREM stage 3%. Furthermore, there was a decrease in daytime sleepiness, measured by the Multiple Sleep Latency Test (MSLT). Harmell and coworkers [37] investigated the impact of OSA and CPAP therapy on *cognitive deterioration* in the same cohort of patients with PD with a follow-up duration of 6 months. Patients with OSA had significantly lower MMSE and MoCA scores at baseline, compared to patients without OSA. However, no effect of CPAP therapy was reported on any domain of a complete neuropsychological evaluation during follow-up.

Meng and coworkers [38] investigated the impact of OSA and CPAP therapy on *motor progression* in 67 patients with PD (20 patients without OSA, 26 patients with OSA, who received CPAP therapy, and 21 patients with OSA, who did not receive CPAP therapy). At baseline, patients with OSA had higher UPDRS part 3 scores than those without OSA. After 1 year of follow-up, UPDRS part 3 and timed up and go (TUG) [41] scores decreased in patients with OSA and CPAP therapy, while patients without OSA and patients with OSA without CPAP therapy had a similar increment in both tests. Kaminska and coworkers investigated the impact of OSA and CPAP therapy on *cognitive deterioration* in the same cohort of patients with PD [39]. There was no significant difference in MoCA score, between patients with OSA and without OSA at baseline. However, after 1-year follow-up, there was a significant improvement in MoCA score in the group treated with CPAP therapy, while MoCA scores remained stable in the group without OSA and the group with OSA without CPAP therapy. The improvement in MoCA score in the CPAP group was only found in patients with baseline cognitive impairment (MoCA score < 26). Furthermore, there was an improvement in Parkinson's Disease Sleeping Scale (PDSS) in the CPAP group and Epworth Sleepiness Scale (ESS) [42] scores remained stable during follow-up.

Terzaghi and coworkers [40] investigated the impact of CPAP therapy on both *cognitive deterioration* and *sleep dysfunction* in 36 patients with PD and OSA. At 3-month follow-up, there was a drop out of 75% of patients, due to CPAP intolerance. In the 9 patients that continued CPAP therapy, there was no significant change in ESS score or neuropsychological evaluation at 3 months. However, the follow-up PSG showed a significant decrease in AHI and a trend toward significance in NREM stage 3% increment.

EEG Variables and Sleep Stages

Five studies investigated the predictive value of EEG-related PSG variables in disease progression prediction in PD [25, 43–46]. Cesari and coworkers investigated PSG predictors of *RBD development*, using an automated data-driven model based on EEG and EOG recordings, in 107 de novo PD patients (54 patients with normal REM sleep, 26 patients with RBD, and 27 patients with RBE without RSWA) [43]. Micro-sleep structure, EEG spectral, EEG coherence, EEG complexity features, and EOG energy features were tested, using machine learning. The final model, which included mainly micro-sleep structure features and EEG spectral features, had a sensitivity and specificity of over 80% in differentiating RBD from nonRBD at baseline. The same model could predict which patients with RBE at baseline developed RBD after 2 years of follow-up (AUC 0.87, sensitivity 77.78%, and specificity 87.5%). However, the model could not predict which patients without RBE developed RBD at follow-up.

Schreiner and coworkers investigated if slow-wave sleep could predict *motor progression* in 129 patients with PD [44]. Slow wave activity (delta power 0.5–4.5 Hz) and slow-wave energy (accumulated power in the slow-wave activity band) in NREM sleep stages 2 and 3 were computed. Patients were classified as high slow-wave energy or low slow-wave energy. After a follow-up of 4.6 years, patients with high slow-wave energy had significantly slower UPDRS-3 increment. The higher slow-wave activity was strongly associated with slower increase of axial UPDRS 3 scores.

Three studies investigated if EEG variables could predict *cognitive deterioration* in PD [25, 45, 46]. First, Latreille and coworkers investigated EEG spectral variables in 58 non-demented patients with PD [45]. After a follow-up of 4.5 years, 18 patients developed dementia. Baseline predictors for the development of dementia are slowing ratios in posterior regions during REM sleep, slowing ratios in temporal regions during wake and lower dominant occipital frequency. In the same cohort, sleep

spindle density and amplitude at baseline were lower in patients who developed dementia [46]. No differences were found in the percentage of slow-wave sleep (NREM stage 3) between patients who developed dementia and those without dementia. Bugalho and coworkers investigated 25 patients with PD and reported that a lower percentage of NREM stage 3 sleep was associated with a MoCA score decrease after a follow-up of 4 years [25].

Other PSG Variables

Two studies investigated the predictive value of the PLMS index in disease progression prediction in PD [25, 26]. Bugalho and coworkers investigated 25 patients with PD and reported that a higher PLMS index at baseline predicted daytime sleepiness increment (measured by SCOPA-SLEEP) after a follow-up of 4 years [25]. No association was found between the PLMS index at baseline and motor progression (UPDRS-3) and cognitive deterioration (MoCA) at follow-up. Mollenhauer and coworkers, however, investigated 135 de novo PD patients and found that after 4 years of follow-up, an elevated PLMS index was a significant predictor of cognitive deterioration (measured by MMSE) [26]. No association between PLMS index at baseline and motor progression at follow-up (measured by UPDRS 3) was found.

Bugalho and coworkers reported no association between total sleep time or sleep efficiency and progression of sleep dysfunction, motor progression of cognitive deterioration in PD [25]. In addition, no studies that investigated changes in heart rate variability, REM density, or body position during sleep as predictors of sleep dysfunction, motor progression, or cognitive deterioration in PD were found.

Discussion

Summary of Findings

Our systematic review describes 19 cohort studies investigating the role of PSG predictors for sleep dysfunction, motor progression, and cognitive dysfunction progression in PD. Their main findings are that (1) RBE, RSWA, and EEG changes (mainly microsleep instability) are predictors of the development of RBD; (2) RBD, RSWA, and lower slow-wave sleep energy predict motor progression; (3) RBD, EEG slowing, and sleep spindles changes are predictors of cognitive deterioration; and (4) OSA is associated with severe motor and cognitive symptoms at baseline, with inconsistent findings on the effect of CPAP therapy for these symptoms.

Sleep Dysfunction

Most of the included studies with sleep dysfunction as the outcome variable investigated the development of RBD in PD [22–24, 31, 43]. The findings of an increase in PSG-confirmed RBD prevalence from 24 to 52% in de novo PD patients after 6 years of follow-up align with RBD prevalences reported in cross-sectional studies and longitudinal studies that investigated RBD without PSG confirmation [47, 48]. The results suggest that RBD does not always precede the onset of motor symptoms in PD and does not follow an "all-or-nothing" principle [22]. Instead, RBD development seems to be a more gradual process caused by neurodegeneration in the locus coeruleus and projecting areas [49]. Both RBE and RSWA are PSG predictors that increase over time and RBE patients also show a specific RBD-related EEG pattern. This is in line with the hypothesis that RBE and RSWA are prodromal features of RBD [16, 50, 51]. The included studies confirmed this hypothesis in patients diagnosed with PD. These results underline the relevance of investigating the role of RBE and RSWA as prodromal RBD and PD biomarkers in patients without a diagnosis of PD or a related disorder. They may help to expand the RBD spectrum and identify more patients with PD or another synucleinopathy in the prediagnostic stage in the future.

Motor Progression

The included studies report the presence of RBD, RSWA, OSA, and decreased slow-wave energy as PSG variables that predict motor progression in PD [27, 38, 44]. The results of RBD as motor progression predictor are consistent with other cohort studies in PD that investigated RBD without PSG confirmation [52–54]. Pagano and coworkers found lower cerebrospinal fluid alpha-synuclein levels and lower striatal [123I] FP-CIT- uptake (in SPECT images) in PD patients with RBD and faster motor progression, suggesting more alpha-synuclein related pathology and dopamine deficits in these patients [52]. This may explain the faster motor progression. Furthermore, previous studies suggested a link between RBD and the non-tremor dominant PD subtype (with more frequent falls and less response to levodopa) that may result in faster motor progression [55, 56]. However, not all studies included in our review found an association between RBD at baseline and motor progression [25, 26], which suggest that besides RBD there are multiple other variables involved in motor progression prediction in PD.

Meng and coworkers report worse motor severity at baseline in patients with PD and OSA [38], consistent with cross-sectional study results [57•]. The relation between PD motor severity and OSA might be bidirectional [57•]: patients with more severe motor symptoms may have worse nocturnal mobility with the tendency to sleep on their back, which is a risk factor for OSA [14]. In return, OSA causes intermittent cerebral

hypoxia, which may result in increased neuroinflammation and oxidative stress at cell level. The substantia nigra is especially prone to hypoxia [58]. OSA also causes sleep fragmentation and reduced slow-wave sleep. In rodent models, manipulation of slow wave sleep influences cerebral alpha-synuclein accumulation [59] and Schreiner and coworkers indeed described less motor progression in PD patients with higher slow-wave sleep energy [44]. Previous research found a positive correlation between EEG delta power and glymphatic system function, that is responsible for clearance of cerebral waste products, such as alpha-synuclein and amyloid-ß [60]. Dysfunction of the glymphatic system has been described in patients with OSA [61] and is hypothesized to aggravate alfa-synuclein pathology and disease progression in PD [62]. Finally, the relation can be indirect, in which OSA causes excessive daytime sleepiness, resulting in worse (motor) performance during the day [57•].

Meng and coworkers report a beneficial effect of CPAP on motor function in PD after 1 year of follow-up (less motor progression), which suggests a stabilizing effect of CPAP therapy on motor function [38]. However, the group with placebo CPAP and the group of patients with PD with OSA showed no differences in motor progression, which weakens the hypothesis that OSA influences motor progression. Since the OSA group had higher motor severity at baseline, an alternative explanation may be that the mUPDRS increases more slowly in advanced disease which may explain the rapid motor progression in the group without OSA [38]. Future longitudinal studies are necessary to investigate the role of OSA and CPAP therapy in motor progression in PD.

Cognitive Deterioration

The included studies report that RBD, OSA, EEG slowing, and sleep spindles changes are PSG predictors of cognitive deterioration in PD [23, 29–31, 37, 39, 45, 46].

RBD as a predictor of cognitive deterioration in PD has been a consistent finding in the included studies as well as in cross-sectional studies and longitudinal studies that investigated RBD without PSG confirmation [52–54, 63]. Both RBD and cognitive decline in PD are associated with cholinergic deficits on acetylcholinesterase [^{11}C]PMP PET scan [64], suggesting that both symptoms might be caused by cholinergic dysfunction. Furthermore, as mentioned above, RBD is associated with a specific malignant PD subtype: characterized by more severe motor symptoms (especially postural instability gait disorder), autonomic dysfunction, RBD, psychiatric symptoms, and cognitive deterioration, with more cerebral atrophy and dopaminergic deficits on neuroimaging, lower cerebrospinal fluid amyloid-ß, and amyloid-ß/t-tau ratios at baseline and with faster motor progression and cognitive decline over the years [65]. This subtype may have an important overlap with dementia with Lewy bodies, in which RBD also is a prominent feature [66, 67]. Early signs of RBD on a PSG in PD or prodromal PD may be the first manifestation of this subtype.

OSA is also associated with more severe cognitive symptoms at baseline, which might be explained by the same mechanisms in which OSA causes more severe motor symptoms in PD [57•]. However, the association between OSA and cognitive symptoms is not restricted to PD, but is also present in the general population and other neurodegenerative diseases such as Alzheimer's disease (AD) [68], so the effect of OSA in PD might not be PD-specific. In AD, studies consistently reported a positive effect of CPAP therapy on cognitive symptoms and less AD pathology progression [68]. However, the included studies in our review showed inconsistent results on the effect of CPAP therapy on cognitive symptoms in PD, ranging from no effect [37, 40] to a mean improvement in MoCA score of 1.7 points after 12 months [39]. These findings suggest that the impact of OSA on PD pathology and the beneficial effect of CPAP therapy is less straightforward than in AD pathology. All studies, however, had small sample sizes and a maximal follow-up of 1 year. Since PD patients with OSA, in general, were included (not specifically patients with MCI or dementia), the latter may not be long enough to measure a longitudinal effect of OSA or a beneficial effect of CPAP therapy on cognitive decline. Future studies with larger sample size, a longer follow-up period, or inclusion of patients with MCI are necessary to investigate the longitudinal impact of OSA (treatment) on cognitive decline in PD.

The predictive value of EEG for cognitive decline and development of dementia in PD has been previously investigated in several quantitative EEG studies that reported a slowing of background EEG frequency with theta or delta band dominance as a predictor of cognitive decline in PD [69–73]. Latreille and coworkers confirmed slowing of EEG spectral frequency on PSG during wake, mainly in posterior and temporal regions, but also during REM sleep as dementia predictors [45]. Besides REM slowing, patients who developed dementia also showed sleep spindle changes at baseline [46]. An increase in theta and delta power is associated with diffuse cortical and subcortical grey matter dysfunction and cholinergic failure [74], which both play an important role in cognitive impairment in PD [75]. Sleep spindles originate from the thalamo-cortical loop, are cholinergic- and GABAergic-driven, and are involved in sleep maintenance, brain plasticity, and memory consolidation [74, 76]. Early findings of REM sleep EEG slowing and sleep spindle changes (lower density and amplitude) in PD may reflect subtle alterations in these regions and the cholinergic system, that are not severe enough yet to cause cognitive symptoms.

Limitations

This systematic review highlights limitations in the current literature about PSG predictors for disease progression in PD. First, there are some discrepancies in findings between the included studies. These discrepancies may be due to methodological differences between studies, such as differences in (small) sample size, study population, follow-up duration, treatment, correction

for possible confounders, and outcome measures. Differences in PSG analysis methods may have also contributed. Cohort studies with larger sample sizes, use of multiple PSG and clinical variables, and a longer follow-up period are necessary to clear up these discrepancies. Furthermore, the discrepancies underline that multiple variables besides the investigated PSG variables are involved in disease progression in PD.

Secondly, most included studies focused on 1 or a few PSG variables. This review, however, describes that several PSG variables are involved in disease progression prediction. Many PSG variables generally make studies vulnerable to publication bias or type 1 errors. Studies that investigate a combination of PSG variables in more advanced analysis models, such as Cesari and coworkers [43], may increase the power of the PSG in disease progression prediction in PD in the future.

Thirdly, although a consistent association between several PSG variables and disease progression was found, the causality of most associations remains unclear. The question remains whether treatment of the specific sleep disorder will significantly influence disease progression in PD. Until now, no disease-modifying PD medication exists so neuroprotective sleep medicine interventions may be of great value. However, the sleep disturbances and PSG alterations may also be part of a malignant disease course in PD without a causal effect.

Fourthly, the PSG might not reflect the complete spectrum of PD-related sleep dysfunction. No studies were included that investigated insomnia, circadian rhythm disorders, or hypersomnia as predictors for disease progression in PD, although both are common symptoms in early PD. The reason for this might be that most studies investigating them probably used different methods (such as questionnaires).

Practical Implications

Our review shows that in the different cohorts (of mainly early PD patients), multiple PSG variables are already abnormal at baseline. The PSG abnormalities also correlate with sleep-related symptoms and other symptoms in PD. These findings highlight the importance of sleep dysfunction in PD. Performing a video-PSG in early PD in the clinical setting may be useful (1) for a comprehensive evaluation of the disease spectrum, (2) to diagnose different sleep and wake disorders in PD (such as RBD and OSA), and (3) for the treatment of these sleep disorders. This might be especially useful in patients with sleep-related symptoms and/or a malignant or atypical disease course.

Conclusions and Future Directions

In conclusion, our review describes that different REM sleep variables, sleep-related breathing variables, and EEG variables on the PSG can predict the progression of sleep dysfunction, motor symptoms, and cognitive decline in PD. The results support a role of the video-PSG in disease progression prediction in PD. Future studies should focus on how these PSG variables can be used as biomarkers in clinical practice in clinical PD and in the prediagnostic PD stages and whether treatment of the PSG abnormalities, such as OSA and RBD will have a neuroprotective effect on disease progression.

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Declarations

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