REVIEW

Impact of Obstructive Sleep Apnea on Cognitive and Motor Functions in Parkinson's Disease

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ABSTRACT: Introduction: Parkinson's disease (PD) is a chronic neurodegenerative disorder that presents with motor and non-motor manifestations. Amongst the non-motor features, various forms of sleep disturbances can occur, and obstructive sleep apnea (OSA) is considered to be a common comorbidity. We conducted this systematic review and meta-analysis to assess the impact of OSA on cognitive and motor functions in PD.

Methods: The information sources of for this systematic review and meta-analysis were PubMed, SCOPUS, Web of Science, and ScienceDirect. Studies meeting the following criteria were included: (1) studies including idiopathic PD patients, (2) studies using polysomnography to categorize PD patients into PD with OSA and PD without OSA, and (3) studies with observational designs (case–control, cohort, or cross-sectional). Data analysis was performed using RevMan.

Results: Our meta-analysis showed that OSA was associated with significantly lower scores of Montreal Cognitive Assessments (MoCA) (mean difference (MD) = −0.70, 95% confidence interval (CI) [−1.28, −0.13], P = 0.01) and Mini-Mental State Examination (MMSE) (MD = −0.69, 95% CI [−1.17, −0.21], P = 0.005). Moreover, the score of the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS III) was significantly higher in PD patients with OSA as compared with those without OSA (MD = 1.63, 95% CI [0.03, 3.23], P = 0.049).

Conclusions: OSA is associated with increased severity of PD-associated cognitive dysfunction and motor symptoms. However, further studies are needed to corroborate these findings, assess the underlying mechanisms by which OSA influences the motor and cognitive functions in PD, and investigate whether OSA can accelerate the neurodegenerative process of PD. © 2020 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; obstructive sleep apnea; cognition; motor function

Introduction

Parkinson's disease (PD) is a common chronic and progressive neurodegenerative disease, with an approximate prevalence of 1% in people above the age of 60 years.[1] It is characterized by both motor and non-motor manifestations, which occur due to the loss of dopaminergic and non-dopaminergic neurons, respectively.[2] The cardinal motor features for which PD is most known include resting tremor, postural instability, bradykinesia, and rigidity.[3] Conversely, the non-motor manifestations of PD are less conspicuous than PD motor symptoms but are associated with significant

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morbidity.[2] PD non-motor symptoms include depression,[4] anxiety,[5] constipation,[6] pain, genitourinary discomfort, and sleep problems,[7] which can be further subclassified into insomnia,[4] excessive daytime sleepiness,[8] rapid eye movement behavior disorder (RBD),[9] restless legs syndrome,[10] and sleep disordered breathing.[11,12] The increased burden of non-motor symptoms in PD patients is associated with increased overall severity of the disease[13] and decreased quality of life.[2,5,14] It also has a negative impact on health economics in this population of patients.[15]

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent upper airway obstruction leading to periodic arrests of breathing during sleep, which result into both intermittent hypoxia and frequent arousal.[16] In OSA, a brief period (lasting for seconds) of oxygen desaturation is immediately followed by oxygen resaturation, which can occur hundreds of times per night. This recurrent and intermittent oxygen desaturation and resaturation lead to increased oxidative stress and generation of reactive oxygen species, which may damage a variety of cells, including dopaminergic neurons in the brain.[17] Oxidative stress may also contribute to a molecular cascade of events such as damage to cellular lipids and proteins, and impaired mitochondrial functions, leading ultimately to dopaminergic neuronal degeneration in PD.[18,19] Clinically, OSA results in symptoms of excessive daytime sleepiness, memory problems, nocturia, and non-refreshing sleep.[16,20] Without proper management, OSA is associated with critical health consequences such as refractory hypertension,[21] cardiovascular diseases,[22] depression, cognitive slowing,[23] metabolic disorders,[20] disturbance of glucose homeostasis/diabetes,[24] and increased risk of ischemic stroke.[25] Therefore, it is important to diagnose OSA in a timely fashion and manage it properly, especially in patients with symptoms suggestive of OSA.

A few recent studies have assessed the risk of OSA in PD patients.[26-29] The results of these studies exhibited a wide variability of OSA prevalence in PD patients, which can be explained by the differences in patient populations, sample sizes, and the scoring system of apnea and hypopnea events.[30,31] The suggested mechanisms that might be implicated in the development of OSA in PD patients include PD-associated autonomic dysfunction that might cause disruption of breathing,[30] involuntary contractions of upper airway muscles leading to airway obstruction,[32] laryngopharyngeal motor dysfunction,[33] levodopa-induced dyskinesia[34,35] and age-related collapsibility of the pharyngeal airway which occurs even independently of body mass index (BMI) and gender.[36,37] Furthermore, a few studies compared PD patients who had OSA (PD + OSA) with PD patients who did not have OSA (PD – OSA), and the comparison included motor and/or cognitive functions.[11,33,38-46] Due to the discrepancy between the results of such studies, we conducted this systematic review and meta-analysis to assess how OSA influences both motor and cognitive functions in PD patients.

Methods

We followed the Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) during the preparation of this article.[47] The study protocol was registered at PROSPERO database (CRD42020202228); https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=202228. The methods and analyses were conducted in strict accordance with the guidelines of the Cochrane Handbook of Systematic Review and Meta-analysis and the Methods Guide for Comparative Effectiveness Reviews.[48,49]

Eligibility Criteria

Studies that met all of the following criteria were included in the meta-analysis: (1) studies including patients with idiopathic PD; (2) studies in which PD patients underwent overnight polysomnography (PSG) to be categorized into PD + OSA and PD – OSA groups, and compared PD + OSA patients to PD – OSA patients in terms of motor and cognitive functions and OSA parameters; and (3) studies that were observational in design (case–control, cohort, or cross-sectional studies). Non-English language and animal studies, case reports, conference abstracts, and review articles were excluded.

Information Source and Literature Search

A computerized search in the following databases: MEDLINE via PubMed, SCOPUS, Web of Science, and ScienceDirect was conducted between January 2020 and July 2020 for the published peer-reviewed articles from inception to July 2020. We used the following keywords: "Obstructive Sleep Apnea", "OSA", "Sleep disorders", "Parkinson's disease", and "PD" (Appendix S1). We did not include any data from grey literature in our systematic review and meta-analysis.

Study Selection

Two independent reviewers (M. Elfil and M. Eldokmak) assessed the retrieved articles using an offline 2016 Microsoft Excel sheet through two steps; titles and abstracts; then, the full-text articles of the eligible abstracts were retrieved for further eligibility screening and assessment of the reliability of data for analysis. Any discrepancies were resolved by a third reviewer (E.I. Bahbah).

Data Collection Process and Data Items

An offline data extraction sheet was constructed. The data extraction included the following domains:

(1) study ID, (2) study year, (3) country, (4) study design, (5) follow-up duration, (6) population definition, (7) sample size, (8) baseline characteristics, (9) available data of outcome measures, and (10) quality assessment domains.

Quality Assessment

The Newcastle–Ottawa Scale (NOS) for observational studies (case–control, cohort, and cross-sectional studies)[50] was used to evaluate the quality of each included study, and this includes eight assessment items for quality appraisal, including "selection", "comparability", and "outcome." According to the NOS score standard, observational studies (case–control, cohort, and cross-sectional) could be classified as low-quality (scores of 0–4), moderate-quality (scores of 5–6), and high-quality (scores ≥7) (Appendix S1).

Assessment of Heterogeneity

Forest plots were inspected visually for any heterogeneity. We assessed the heterogeneity using the I-square (I^2) and Chi-square (Chi^2) tests. For the Chi^2 test of the Q-statistics, an alpha level below 0.1 was considered for significant heterogeneity. To quantify the magnitude of heterogeneity among effect estimates of the included studies, we interpreted the I^2 test results as the follows: values from 0% to 30% as being likely minimal, values from 30% to 60% as likely moderate, and values from 60% to 100% as likely substantial heterogeneity.

Synthesis of Results

Because the majority of outcomes were reported as continuous data, for each measure, the mean difference (MD) between the two groups with its standard deviation (SD) were pooled in the DerSimonian–Laird fixed- and random-effect models. The overall MD was interpreted with the consideration that measures are in different directions; worsening of the overall Unified Parkinson's Disease Rating Scale (UPDRS), UPDRS III, and Hoehn and Yahr (H&Y) scale is indicated by increased MD while worsening of the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessments (MoCA) is indicated by decreased MD. For the OSA and sleep parameters, we analyzed the following parameters: total sleep time (TST), Parkinson's Disease Sleep Scale (PDSS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), apnea–hypopnea index (AHI), oxygen desaturation index (ODI), rapid eye movement (REM) sleep, non-REM sleep stages N1, N2, and N3, sleep efficiency, sleep latency, awakening, wake after sleep onset, respiratory arousal index (RAI), and periodic leg movement (PLM) index. Sensitivity analysis was applied according to the sequential algorithm method.[51] Data analysis was performed using RevMan version 5.3 for Windows.

Results

Study Selection

The literature search of databases yielded 1380 records. Following the title/abstract and full-text screening, 11 articles with a total of 1069 patients (474 with OSA and 595 without OSA) were included in the

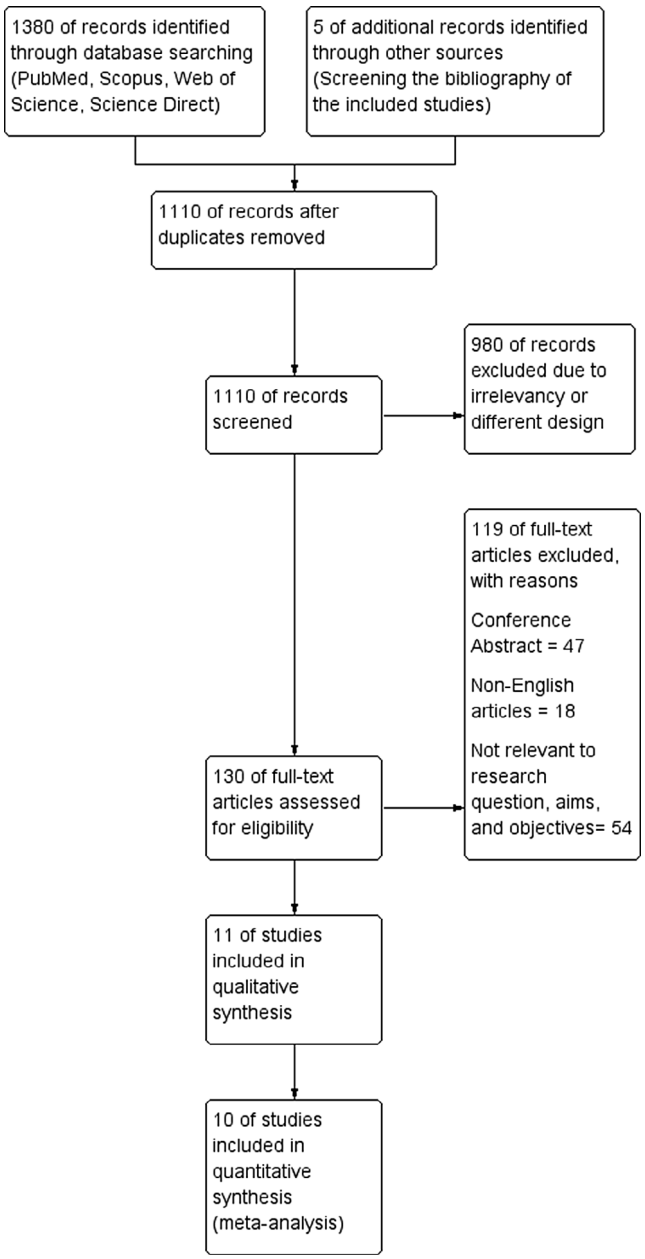

FIG. 1. PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analysis) flow diagram showing the process of study selection. The literature search of databases yielded 1380 records. Following title/abstract and full-text screening, 11 articles were included in the systematic review and meta-analysis.

systematic review and meta-analysis. The flow of the study selection process is shown in the PRISMA flow diagram in Figure 1.

Patients and Study Characteristics

The majority of the included studies were conducted in high-income countries; three studies in Canada, two in China, two in Brazil, one in the United States, one in France, one in Japan, and one in Switzerland. Six studies were cross-sectional, three studies were prospective cohort, one study was retrospective, and one study was case–control. The mean age of the included populations was 64.5 (57–72.5) years. The majority of included patients were males. The average BMI was 25.82 kg/m^2. The mean duration of PD from diagnosis was 6.6 years. There were no significant differences between PD + OSA patients and PD – OSA patients in terms of age (64.85 years for the PD + OSA group and 63.35 years for the PD – OSA group, P = 0.416), BMI (26.4 kg/m^2 for the PD + OSA group and 25.20 kg/m^2 for the PD – OSA group, P = 0.101), and PD duration (6.19 years for the PD + OSA group and 6.18 years for the PD – OSA group, P = 0.991). Four studies reported associated comorbidities such as diabetes, hypertension, and heart diseases.[33,38,44,46] An overlap between Mery (2017), Kaminska (2018), and Meng (2020) was detected. Therefore, we extracted unique outcomes from each study, and in case of repetition, we used the most updated study Meng (2020). Table 1 shows the baseline characteristics of the included studies and patients, respectively.

Quality of Included Studies

The quality of included studies was very good for cross-sectional studies, and good for both cohort and case–control studies in terms of selecting patients and controls, comparability, and outcomes assessment and follow-up. The quality of the included studies assessed by the NOS tool is presented in Appendix S1.

Meta-Analysis Findings

All findings of the meta-analysis are presented in Table 2.

PD Severity: UPDRS and H&Y Scale

Two studies[42,45] (n = 151 patients) reported the overall UPDRS, and the overall fixed-effect estimate showed that the overall-UPDRS score was significantly higher in the PD + OSA group than in the PD – OSA group (MD = 3.84, 95% CI [0.07, 7.61], P = 0.049). However, the random-effect model showed that the overall-UPDRS score was comparable in both groups (P = 0.49). Pooled studies were not homogenous (P = 0.01, I^2 = 77%). A sensitivity analysis was not applicable.

Seven studies[11,33,38-40,42,43] assessed UPDRS III in PD + OSA patients in comparison with PD – OSA ones. The random-effect estimate of these seven studies (n = 738 patients) demonstrated that the UPDRS III score was significantly higher in the PD + OSA group (MD = 1.63, 95% CI [0.03, 3.23], P = 0.049). Pooled data were homogenous (I^2 = 26%, P = 0.23).

Two studies[42,45] assessed UPDRS I. The pooled analysis of these two studies (n = 151 patients) demonstrated that there was no significant difference between both groups in terms of UPDRS I (MD = 0.40, 95% CI [−0.65, 1.44], P = 0.46). Pooled data were homogenous (I^2 = 0%, P = 0.51).

H&Y scale was assessed in eight studies.[33,38-41,43-45] The overall fixed-effect estimate of these eight studies (n = 813 patients) showed that there was no significant difference between PD + OSA patients and PD – OSA patients in terms of the H&Y scale (MD = 0.06, 95% CI [−0.04, 0.15], P = 0.26). Pooled studies were not homogenous (P = 0.05, I^2 = 50%). Heterogeneity was best resolved by excluding the study of Shen (2020) (P = 0.18, I^2 = 33%). Following the resolution of heterogeneity, the random-effect estimate showed that the PD + OSA group had a higher score on the H&Y scale than the PD – OSA group (MD = 0.18, 95% CI [0.0, 0.23], P = 0.04).

Additionally, data from nine studies[11,33,38-44] (n = 875 patients) showed that PD + OSA patients were on a lower level of L-dopa equivalent dose (MD = −58.63 mg/dL, 95% CI [−103.93, −13.34], P = 0.01). Pooled studies were not homogenous (P = 0.01, I^2 = 58%). Heterogeneity was best resolved by excluding the study of Shen (2020) (P = 0.95, I^2 = 0%). After the resolution of heterogeneity, the random-effect estimate showed that there was no significant difference between both groups (MD = 5.72 mg/dL, 95% CI [−48.93, 60.36], P = 0.84).

Cognitive Assessments

The pooled analysis of three studies[38-40] (n = 501) demonstrated that compared with the PD – OSA group, the PD + OSA group had a significantly lower mean MMSE score (MD = −0.69, 95% CI [−1.17, −0.21], P = 0.005). Pooled data were homogenous (I^2 = 14%, P = 0.31). Furthermore, the pooled analysis of four studies[38,40,42,45] (n = 564 patients) showed that the PD + OSA group had a significantly lower average MoCA score than the PD – OSA group (MD = −0.70, 95% CI [−1.28, −0.13], P = 0.01). Pooled data were homogenous (I^2 = 29%, P = 0.24).

Subjective Sleep Assessments

The pooled analysis of two studies[38,39] (n = 327 patients) showed that there was no significant difference between both groups in terms of PSQI (MD = −0.64,

TABLE 1. Baseline characteristics of the included studies

Study ID	Country	Design	Population	Age (mean (SD))	Male (%)	BMI (mean (SD))	Disease time from diagnosis (mean years ± SD, median (IQR))	Comorbidities (n (%))	PD diagnosis criteria	OSA diagnosis criteria	Levodopa equivalent dose
Bahia 2018[33]	Brazil	Cross-sectional	PD + OSA (n = 31)	62.8 (10.1)	41 (85.4)	26.2 (4.1)	8.4 ± 4.1	NA	UK PDS Brain Bank criteria[a]	RDI ≥5	738.9 ± 321.5
			PD - OSA (n = 17)	63.3 (11)		25.5 (3.1)	6.5 ± 4.3				658.1 ± 453.7
Cohen De Cock 2015[41]	France	Cross-sectional	PD + OSA (n = 15)	66 (6)	13 (87)	27 (6)	8.3 ± 5.8	NA	UK PDS Brain Bank criteria[a]	AHI ≥5 episodes/hr on PSG	616 ± 364
			PD - OSA (n = 15)	66 (6)	13 (87)	25 (3)	8.1 ± 6.1				673 ± 385
Huang 2018[40]	China	Prospective cohort	PD + OSA (n = 60)	66 (7.5)	41 (68.33)	24.8 (3.1)	3 (2–4)	NA	UK PDS Brain Bank criteria[a]	AHI ≥5 episodes/hr on PSG	320.05 ± 30.14
			PD - OSA (n = 114)	63.8 (7.7)	72 (63.16)	23.6 (2.9)	3 (1–6)				310.67 ± 22.67
Kaminska 2018[45]	Canada	Prospective cohort	PD + OSA (n = 46)	66.0 (10.2)	29 (63)	28.6 (4.4)	NA	NA	UK PDS Brain Bank criteria[a]	AHI ≥15 episodes/hr on PSG	710.4 ± 771.8
			PD - OSA (n = 19)	60.7 (8.2)	11 (58)	26.2 (3.2)					802.9 ± 608.5
Meng 2020[12]	Canada	Prospective cohort	PD + OSA (n = 47)	61.5 (8.4)	12 (60.0)	26.1 (3.3)	5.4 ± 3.5	3 (15.0)	UK PDS Brain Bank criteria[a]	AHI ≥15 episodes/hr on PSG	848.7 ± 1050.4
			PD - OSA (n = 20)	64.6 (10.8)	11 (52.4)	27.5 (4.2)	6.6 ± 5.9	13 (61.9)			789.8 ± 616.9
Mery 2017[46]	Canada	Cross-sectional	PD + OSA (n = 47)	65.7 (10.3)	29 (61.7)	28.5 (4.4)	6.4 ± 6.9	32 (68.1)	UK PDS Brain Bank criteria[a]	AHI ≥15 episodes/hr on PSG	709.7 ± 763.4
			PD - OSA (n = 20)	61.2 (8.3)	12 (60)	26 (3.3)	5.5 ± 3.4	9 (20)			777.8 ± 602.9
Neikrug 2013[42]	USA	Cross-sectional	PD + OSA (n = 47)	68.1 (9.4)	34 (72.3)	27.2 (4.2)	6 ± 5.5	NA	NA	AHI ≥10 episodes/hr on PSG	853.3 ± 661.8
			PD - OSA (n = 39)	66.6 (9)	23 (58.97)	26.3 (4.2)	6.5 ± 5.2				852.8 ± 534.9
Sobreira-Neto 2019[39]	Brazil	Cross-sectional	PD + OSA (n = 55)	63 (12)	37 (67.3)	25 (5)	8.53 ± 5.5	NA	NA	AHI ≥5 episodes/hr on PSG	798 ± 424
			PD - OSA (n = 33)	57 (10)	18 (54.5)	25 (4)	8.33 ± 4.6				912 ± 474
Nomura 2013[44]	Japan	Cross-sectional	PD + OSA (n = 24)	67.9 (7.6)	10 (41.6)	23.4 (4.1)	6.7 ± 7.1	17 (70.833)	NA	AHI ≥15 episodes/hr on PSG	328 ± 232
			PD-OSA (n = 83)	72.7 (8.2)	36 (43.37)	22 (3.5)	7.1 ± 6.7	40 (48.19)			312 ± 217
Shen 2020[38]	China	Retrospective cohort	PD + OSA (n = 66)	67.86 (9.23)	51 (77.3)	NA	3 (1.75–6)	64 (97)	UK PDS Brain Bank criteria[a]	AHI ≥5 episodes/hr on PSG	100 (0, 300)
			PD - OSA (n = 173)	62.76 (10.85)	106 (61.3)	NA	4 (2–6)	95 (61.8)			300 (0, 550)

(Continues)

TABLE 1. Continued

Study ID	Country	Design	Population	Age (mean (SD))	Male (%)	BMI (mean (SD))	Disease time from diagnosis (mean years ± SD, median (IQR))	Comorbidities (n (%))	PD diagnosis criteria	OSA diagnosis criteria	Levodopa equivalent dose
Valko 2012[43]	Switzerland	Case–control	Control (n = 62) PD (n = 62)	59 (6) 58 (6)	20 (67) 19 (54)	28 (4.9) 22.6 (3.1)	8.1 ± 6.9 7.2 ± 4.4	NA	International diagnostic criteria[b]	AHI ≥5 episodes/hr on PSG	NA

[a]Clarke CE, Patel S, Ives N, Rick CE, Woolley R, Wheatley K, et al. UK Parkinson's Disease Society Brain Bank Diagnostic Criteria: NIHR Journals Library; 2016/08.
[b]Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol. 1999;56(1):33–9.
Abbreviations: BMI, body mass index; SD, standard deviation; IQR, interquartile range; PD, Parkinson's disease; OSA, obstructive sleep apnea; NA, not available; UK, United Kingdom; PDS, Parkinson's Disease Society; RDI, respiratory disturbance index; AHI; apnea–hypopnea index; PSG, polysomnography; USA, United State of America.

95% CI [−1.64, 0.36], P = 0.21). Pooled data were homogenous (I^2 = 0%, P = 0.62).

In the same direction, the overall fixed-effect estimate of two studies[42,45] (n = 151 patients) showed that there was no significant difference between PD + OSA and PD − OSA groups in terms of PDSS (MD = 1.53, 95% CI [−5.50, 8.55], P = 0.67). Pooled studies were homogenous (I^2 = 10%, P = 0.29).

The pooled analysis of nine studies[33,38-45] (n = 899 patients) showed that the PD + OSA group had a higher score of ESS as compared with the PD − OSA group (MD = 0.74, 95% CI [0.10, 1.39], P = 0.02). Pooled data were homogenous (I^2 = 16%, P = 0.30).

Objective Sleep Measures

The pooled analysis of seven studies[11,38-41,43,44] (n = 741 patients) showed that the PD + OSA group had higher TST compared with the PD − OSA group (MD = 14.70 min, 95% CI [0.58, 28.83], P = 0.04). Pooled data were homogenous (I^2 = 0%, P = 0.58).

Interestingly, the pooled analysis of six studies[11,38-41,43] (n = 634 patients) showed that the PD + OSA group had better sleep efficiency compared with the PD − OSA group (MD = 4.02%, 95% CI [1.24, 6.81], P = 0.005). Pooled data were homogenous (I^2 = 0%, P = 0.57). However, the overall fixed-effect estimate of three studies (n = 501 patients) showed that there was no significant difference between the PD + OSA and PD − OSA groups in terms of sleep latency (MD = −2.04 min, 95% CI [−6.14, 2.06], P = 0.33). Pooled studies were homogenous (I^2 = 0%, P = 0.86).

The overall fixed-effect estimate of three studies[11,40,43] (n = 277 patients) showed that the PD + OSA group had higher frequency of awakenings than the PD − OSA group (MD = 1.74%, 95% CI [−0.67, 5.16]). However, the difference was not significant between both groups (P = 0.32). Pooled studies were homogenous (I^2 = 17%, P = 0.30). Moreover, the wake after sleep onset was comparable between both groups in the pooled analysis of three studies[39,44,45] (MD = −0.75 min, 95% CI [−7.20, 5.71], P = 0.82). Pooled studies were homogenous (I^2 = 0%, P = 0.96).

Sleep Architecture

The overall fixed-effect estimate of two studies[38,39] (n = 327 patients) showed that there was no significant difference between the PD + OSA group and the PD − OSA group in terms of the duration of REM sleep (MD = 10.53 min, 95% CI [−0.10, 21.16], P = 0.05). Pooled studies were homogenous (I^2 = 0%, P = 0.86). Conversely, the overall fixed-effect estimate of seven studies[11,38-41,43,44] (n = 741) demonstrated that the proportion (%) of REM was comparable between both groups (MD = −0.03%, 95% CI [−0.86, 0.80], P = 0.94). Pooled data were heterogenous (I^2 = 65%,

TABLE 2. Findings of the meta-analysis

Outcome	Studies (patients)	Statistical method	Effect size	*P* value	Heterogeneity test
Overall UPDRS	2 (151)	MD (IV, fixed, 95% CI)	3.84 [0.07, 7.61]	**0.049**	$Chi^2 = 6.70$ ($I^2 = 85\%$, $P = 0.01$)
		MD (IV, random, 95% CI)	3.47 [−6.33, 13.26]	0.49	
UPDRS III	7 (738)	MD (IV, fixed, 95% CI)	1.63 [0.03, 3.23]	0.049	$Chi^2 = 8.07$ ($I^2 = 26\%$, $P = 0.23$)
		MD (IV, random, 95% CI)	1.90 [0.05, 3.84]	0.06	
UPDRS I	2 (151)	MD (IV, fixed, 95% CI)	0.40 [−0.65, 1.44]	0.46	$Chi^2 = 0.43$ ($I^2 = 0\%$, $P = 0.51$)
		MD (IV, random, 95% CI)			
H&Y scale	8 (813)	MD (IV, fixed, 95% CI)	0.06 [−0.04, 0.15]	0.26	$Chi^2 = 13.88$ ($I^2 = 50\%$, $P = 0.05$)
		MD (IV, random, 95% CI)	0.10 [−0.04, 0.25]	0.17	
Levodopa equivalent dose (mg/dL)	9 (875)	MD (IV, fixed, 95% CI)	−58.63 [−103.93, −13.34]	**0.01**	$Chi^2 = 19.20$ ($I^2 = 58\%$, $P = 0.01$)
		MD (IV, random, 95% CI)	−31.67 [−115.75, 52.42]	0.46	
MMSE	3 (501)	MD (IV, fixed, 95% CI)	−0.69 [−1.17, −0.21]	**0.005**	$Chi^2 = 2.33$ ($I^2 = 14\%$, $P = 0.31$)
		MD (IV, random, 95% CI)	−0.67 [−1.20, −0.13]	**0.02**	
MoCA	4 (564)	MD (IV, fixed, 95% CI)	−0.70 [−1.28, −0.13]	**0.01**	$Chi^2 = 4.21$ ($I^2 = 29\%$, $P = 0.24$)
		MD (IV, random, 95% CI)	−0.73 [−1.45, −0.01]	**0.049**	
PSQI	2 (327)	MD (IV, fixed, 95% CI)	−0.64 [−1.64, 0.36]	0.21	$Chi^2 = 0.25$ ($I^2 = 0\%$, $P = 0.62$)
		MD (IV, random, 95% CI)			
PDQ-39	2 (174)	MD (IV, fixed, 95% CI)	0.63 [−4.06, 5.32]	0.79	$Chi^2 = 0.35$ ($I^2 = 0\%$, $P = 0.55$)
		MD (IV, random, 95% CI)			
Parkinson's Disease Sleep Scale	2 (151)	MD (IV, fixed, 95% CI)	1.53 [−5.50, 8.55]	0.67	$Chi^2 = 1.12$ ($I^2 = 10\%$, $P = 0.29$)
		MD (IV, random, 95% CI)	1.43 [−6.04, 8.90]	0.71	
Fatigue Severity Scale	2 (304)	MD (IV, fixed, 95% CI)	−0.02 [−0.40, 0.36]	0.91	$Chi^2 = 0.04$ ($I^2 = 0\%$, $P = 0.83$)
		MD (IV, random, 95% CI)			
Hamilton Rating Scale for Depression	2 (413)	MD (IV, fixed, 95% CI)	−1.01 [−2.39, 0.36]	0.15	$Chi^2 = 2.97$ ($I^2 = 33\%$, $P = 0.23$)
		MD (IV, random, 95% CI)	−1.01 [−2.97, 0.95]	0.31	
ESS	9 (899)	MD (IV, fixed, 95% CI)	0.74 [0.10, 1.39]	0.02	$Chi^2 = 9.50$ ($I^2 = 16\%$, $P = 0.30$)
		MD (IV, random, 95% CI)	0.79 [0.06, 1.51]	0.03	
TST	7 (741)	MD (IV, fixed, 95% CI)	14.70 [0.58, 28.83]	**0.04**	$Chi^2 = 4.69$ ($I^2 = 0\%$, $P = 0.58$)
		MD (IV, random, 95% CI)			
Sleep efficiency	6 (634)	MD (IV, fixed, 95% CI)	4.02 [1.24, 6.81]	**0.005**	$Chi^2 = 3.87$ ($I^2 = 0\%$, $P = 0.57$)
		MD (IV, random, 95% CI)			
Sleep latency (min)	3 (501)	MD (IV, fixed, 95% CI)	−2.04 [−6.14, 2.06]	0.33	$Chi^2 = 0.30$ ($I^2 = 0\%$, $P = 0.86$)
		MD (IV, random, 95% CI)			
Awakenings (%)	3 (277)	MD (IV, fixed, 95% CI)	1.64 [−1.08, 4.36]	0.32	$Chi^2 = 2.42$ ($I^2 = 17\%$, $P = 0.30$)
		MD (IV, random, 95% CI)	1.74 [−0.67, 5.16]	0.24	
Wake after sleep onset (min)	3 (260)	MD (IV, fixed, 95% CI)	−0.75 [−7.20, 5.71]	0.82	$Chi^2 = 0.08$($I^2 = 0\%$, $P = 0.96$)
		MD (IV, random, 95% CI)			
Non-REM N1 stage (%)	5 (537)	MD (IV, fixed, 95% CI)	2.59 [0.83, 4.35]	**0.004**	$Chi^2 = 4.77$ ($I^2 = 16\%$, $P = 0.31$)
		MD (IV, random, 95% CI)	2.63 [0.70, 4.57]	**0.008**	
Non-REM N2 stage (%)	5 (537)	MD (IV, fixed, 95% CI)	0.17 [−2.35, 2.70]	0.89	$Chi^2 = 3.66$($I^2 = 0\%$, $P = 0.45$)
		MD (IV, random, 95% CI)			
Non-REM N3 stage (%)	7 (741)	MD (IV, fixed, 95% CI)	−1.13 [−1.94, −0.32]	**0.006**	$Chi^2 = 31$($I^2 = 81\%$, $P = 0.0001$)
		MD (IV, random, 95% CI)	−2.60 [−5.04, −0.16]	0.04	
REM sleep duration (min)	2 (327)	MD (IV, fixed, 95% CI)	10.53 [−0.10, 21.16]	0.05	$Chi^2 = 0.03$($I^2 = 0\%$, $P = 0.86$)
		MD (IV, random, 95% CI)			
REM (%)	7 (741)	MD (IV, fixed, 95% CI)	−0.03 [−0.86, 0.80]	0.94	$Chi^2 = 17.18$ ($I^2 = 65\%$, $P = 0.009$)
		MD (IV, random, 95% CI)	−0.01 [−1.89, 1.88]	0.99	
AHI (/hr)	6 (526)	MD (IV, fixed, 95% CI)	20.5 [18.18, 22.84]	< 0.00001	$Chi^2 = 30.97$ ($I^2 = 84\%$, $P < 0.00001$)
		MD (IV, random, 95% CI)	22.69 [16.59, 28.79]	**< 0.00001**	
ODI	3 (303)	MD (IV, fixed, 95% CI)	8.38 [7.50, 9.26]	< 0.00001	$Chi^2 = 4.70$ ($I^2 = 57\%$, $P = 0.10$)
		MD (IV, random, 95% CI)	7.70 [5.52, 9.89]		
RAI	3 (387)	MD (IV, fixed, 95% CI)	2.68 [2.18, 3.19]	**< 0.00001**	$Chi^2 = 54.26$ ($I^2 = 96\%$, $P < 0.0001$)
		MD (IV, random, 95% CI)	11.19 [−0.47, 22.86]	0.06	
PLM index in sleep	3 (331)	MD (IV, fixed, 95% CI)	−9.78 [−14.92, −4.63]	0.0002	$Chi^2 = 12.69$ ($I^2 = 84\%$, $P = 0.002$)
		MD (IV, random, 95% CI)	−0.27 [−20.43, 19.88]	0.98	

Note: Bold type indicates statistical significance.
Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; MD, mean difference; IV, inverse variance; CI, confidence interval; H&Y scale, Hoehn and Yahr scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; PDQ-39, Parkinson's Disease Questionnaire-39; ESS, Epworth Sleepiness Scale; TST, total sleep time; non-REM, non-rapid eye movement; REM, rapid eye movement; AHI, apnea–hypopnea index; ODI, overnight desaturation index; RAI, respiratory arousal index; PLM, periodic leg movement index.

$P = 0.009$). Heterogeneity was best resolved by excluding the study of Cohen De Cock (2015) and Nomura (2013) ($P = 0.36$, $I^2 = 8\%$). After resolving heterogeneity, the random-effect estimate was still not significant (MD = 0.40%, 95% CI [−0.65, 1.45], $P = 0.45$). The pooled analysis of five studies[11,38,39,43,44] (n = 537 patients) showed that the PD + OSA group had a longer duration (represented by %) of non-REM N1 sleep stage as compared with the PD − OSA group (MD = 2.59%, 95% CI [0.83, 4.35], $P = 0.004$). Pooled data were homogenous ($I^2 = 16\%$, $P = 0.31$). However, in terms of non-REM N2 stage, there was no significant difference between the two groups (MD = 0.17%, 95% CI [−2.35, 2.70], $P = 0.89$). Pooled data were homogenous ($I^2 = 0\%$, $P = 0.44$). Regarding the non-REM N3 stage, the pooled analysis of seven[11,38-41,43,44] studies demonstrated that the PD + OSA group had a shorter N3 stage (MD = −2.60%, 95% CI [−5.04, −0.16], $P = 0.04$). Pooled data were heterogenous ($I^2 = 81\%$, $P = 0.0001$). Heterogeneity was best resolved by excluding the study of Huang (2018), Shen (2020), and Nomura (2013) ($P = 0.40$, $I^2 = 0\%$). Following the resolution of heterogeneity, the random-effect estimate remained significant (MD = −5.78%, 95% CI [−8.59, −2.97], $P < 0.0001$).

Breathing Assessments

The pooled analysis of six studies[11,39-42,44] (n = 526 patients) showed that the PD + OSA group had a higher AHI compared with the PD − OSA group (MD = 20.5/hr, 95% CI [18.18, 22.84], $P < 0.00001$). Pooled data were not homogenous ($I^2 = 84\%$, $P < 0.00001$). Heterogeneity was best resolved by excluding Cohen De Cock (2015) and Huang (2018) ($I^2 = 41\%$, $P = 0.16$). After resolving heterogeneity, the random-effect estimate remained significant (MD = 22.80/hr, 95% CI [19.09, 26.51], $P < 0.00001$).

The pooled analysis of three studies[11,40,44] (n = 303 patients) showed that the PD + OSA group had a higher ODI compared with the PD − OSA group (MD = 7.70, 95% CI [5.52, 9.89], $P < 0.00001$). Pooled data were homogenous ($I^2 = 57\%$, $P = 10$).

The pooled analysis of three studies[11,38,44] (n = 387 patients) showed that the PD + OSA group had a higher RAI compared with the PD − OSA group (MD = 2.68, 95% CI [2.18, 3.19], $P < 0.00001$). Pooled data were not homogenous ($I^2 = 96\%$, $P < 0.00001$). A sensitivity analysis was not applicable.

PLM Index in Sleep

The pooled analysis of three studies[38,41,43] (n = 331 patients) showed that the PD + OSA group had a higher PLM index in sleep compared with the PD − OSA group (MD = −9.78, 95% CI [−14.92, −4.63], $P < 0.0002$). Pooled data were not homogenous ($I^2 = 84\%$, $P = 0.002$). Heterogeneity was best resolved by excluding Shen (2019) ($I^2 = 0\%$, $P = 0.65$). After resolving heterogeneity, the random-effect estimate showed non-significant results (MD = 10.60, 95% CI [−1.82, 23.02], $P = 0.09$).

Comorbidities

The pooled analysis of three studies[38,44,46] showed that PD + OSA patients had a two-time higher risk of heart diseases than the PD − OSA group (OR = 2.08, 95% CI [1.05, 4.09], $P = 0.03$). Pooled data were homogenous ($I^2 = 0\%$, $P = 0.76$) (Appendix S1, Fig. S1). In terms of hypertension, the data pooled from four studies[33,38,44,46] demonstrated that PD + OSA patients had also a two-time higher risk of hypertension compared with PD − OSA patients (OR = 2.19, 95% CI [1.38, 3.46], $P = 0.0008$). Pooled data were homogenous ($I^2 = 0\%$, $P = 0.43$) (Appendix S1, Fig. S2). The pooled analysis of two studies[38,46] showed that both groups had similar risks of diabetes mellitus (OR = 0.86, 95% CI [0.27, 2.70], $P = 0.80$). Pooled data were homogenous ($I^2 = 0\%$, $P = 0.49$) (Appendix S1, Fig. S3).

Discussion

Our systematic review and meta-analysis aimed to assess the impact of OSA on both motor and cognitive functions in PD patients. We took into consideration the absence of agreement between the results of the previous comparative studies that assessed motor and/or cognitive functions in PD patients with and without OSA, whether as primary outcomes or secondary ones. Our results revealed significant differences between PD + OSA patients and PD − OSA patients in MoCA, MMSE, and UPDRS III scores, which can be interpreted as worse cognitive and motor functions in PD + OSA patients as compared with PD − OSA patients.

Since there are currently no disease-modifying treatments available for PD,[52] it is very crucial to identify and address the factors that can contribute to speeding up the disease progression and/or worsening of the PD motor and non-motor symptoms. OSA might have the potential to worsen PD motor symptoms, and such worsening in turn increases the risk of disability in those patients.[53] This study sheds light on the importance of understanding OSA as a comorbidity that may cause worsening of PD motor and non-motor symptoms. Based on such an interaction between OSA and PD, there is a need to assess the impact of OSA treatment, typically continuous positive airway pressure (CPAP), on PD in terms of alleviating symptoms severity and disease progression.

PD is associated with cognitive impairment, and almost 50% of PD patients with normal baseline cognitive function at the time of PD diagnosis develop cognitive impairment within 6 years of follow-up.[54] OSA is also associated with cognitive dysfunction in the general population, including declines in working memory, attention, and executive functions.[55] In our meta-analysis, PD + OSA patients showed significantly lower scores of both MoCA and MMSE compared with PD – OSA patients, which suggests that OSA can worsen cognition in PD patients, even independently from PD-associated cognitive decline. This decline in PD + OSA patients' cognitive function might be partially explained by sleep fragmentation and hypoxemia, which can cause malfunction of locus coeruleus and multiple other brain areas.[42] Additionally, OSA triggers global neuroinflammation in the central nervous system, which affects brainstem nuclei and contributes to the cognitive impairment noticed in OSA patients.[56] Also, it is to be noted that our results showed that the non-REM N3 sleep stage was of a lower percentage in the PD + OSA group. Non-REM N3 is known to be the slow-wave sleep (SWS),[57] and the reduction of this sleep stage is associated with a higher risk of cognitive decline.[58,59] Another mechanism by which OSA may influence cognition in PD patients is via increasing the risk of certain comorbidities, including mainly hypertension and heart diseases, as better cardiovascular health was found to be directly associated with better cognitive functions.[60] Our meta-analysis found a significantly higher risk of heart diseases and hypertension in PD + OSA patients than in PD – OSA patients. While the definitive biological pathways by which heart diseases can cause cognitive impairment are still unclear, it is to be noted that many risk factors are shared between heart diseases and cognitive impairment, including hypertension and obesity.[61,62] Moreover, hypertension itself has been linked to increased risk of cognitive impairment[63] via mediating changes in the cerebral vasculature and triggering endothelial dysfunction, which can eventually lead to cerebrovascular diseases, cerebral atrophy, and white matter damage.[64]

Our meta-analysis also showed that PD + OSA patients had significantly higher scores of overall UPDRS and UPDRS III when compared with PD – OSA patients. While only one study[11] from those included in our meta-analysis showed a significantly higher UPDRS III score in PD + OSA patients than in PD – OSA patients, the results of the remaining six studies[33,38-40,42,43] were not consistent with this finding. Nevertheless, it is to be taken into consideration that from these seven studies, only two studies[11,38] reported that their PD + OSA patients were not on active CPAP treatment for OSA, while the rest of the studies did not indicate whether or not PD + OSA patients were on CPAP treatment which is associated with less deterioration of the motor function (UPDRS III) in PD patients suffering from OSA.[11] The hypothesized association between OSA and worsening of motor function in PD might be due to sleep fragmentation and hypoxemia caused by OSA, leading to worsening of PD motor symptoms.[46] Besides, cognitive impairment itself was found to be associated with worsening of motor function in PD patients,[65,66] and increased cognitive load was reported to aggravate tremors in PD.[67] This suggests that OSA-induced cognitive decline in PD + OSA patients might be a contributing factor to the deterioration of motor function.

Interestingly, the motor dysfunction itself in PD patients might lead to the development of OSA. Gros and colleagues[68] reported improvement of AHI in PD + OSA patients taking bedtime controlled-release L-dopa, which suggests that PD patients with worse motor symptoms might have a higher risk of OSA.[68] Given these findings, there might be a bidirectional interaction between PD and OSA that allows for cross-talking between the underlying pathological changes of both diseases.

In terms of sleep parameters, our meta-analysis unexpectedly showed that PD + OSA patients had longer TST and better sleep efficiency than PD – OSA patients. The biological mechanisms that can explain such surprising differences are not fully understood yet. However, it is to be noted that our results also revealed that PD + OSA patients were on a lower L-dopa equivalent dose than PD – OSA patients. Increased L-dopa equivalent dose has been reported to be negatively associated with TST in PD patients.[69]

To summarize, our results show that OSA is associated with significantly more severe cognitive deficits and motor symptoms in PD patients. Nonetheless, longitudinal studies are still needed to evaluate whether or not OSA is causal to cognitive and/or motor worsening, while also studying the impact of OSA on motor and cognitive functions in the long term. Such studies should also have more detailed neuropsychological testing to assess which cognitive domains in PD are affected by OSA and which of these domains might be associated with changes in the motor function. Furthermore, it is recommended for future studies looking at the impact of OSA on the motor function in PD patients not to only use UPDRS III, but also to perform the Timed Up and Go (TUG) test to assess gait and balance independently as it might actually be a more accurate assessment of functional status than UPDRS III.[33,70] Finally, there is also a need for interventional studies to assess how the treatment of OSA in PD patients might influence the severity and progression of PD clinical symptoms.

Strengths and Limitations

This is the first meta-analysis to summarize the evidence regarding OSA's impact on cognitive and motor

functions in PD, revealing a significant difference between PD + OSA patients and PD – OSA patients in these regards. However, our study still has some limitations such as: (1) many of the parameters measured, including cognitive assessments (MoCA and MMSE), were only available in a few studies; (2) we excluded patients treated with CPAP if it was clearly mentioned in the study, due to the shortage of data and to suppress all confounders and effect modifiers; (3) we could not perform subgroup analysis according to the severity of OSA or the diagnostic criteria of PD due to the lack of required data; and (4) some outcomes showed a moderate level of heterogeneity due to the difference between the included studies in terms of study design and OSA diagnostic criteria. However, we performed a sensitivity analysis, whenever it was applicable.

Conclusions

OSA is prevalent in PD, and is also associated with increased severity of PD cognitive decline as well as aggravation of PD motor manifestations. Although there is no direct evidence that OSA worsens neurodegeneration and thus symptoms of PD, there is a rationale in that OSA is associated with increasing oxidative stress, which could accelerate neurodegeneration. It is recommended that clinicians maintain a low threshold for assessing the presence of OSA in PD patients to avoid the potential for such accelerated deterioration of PD clinical features. More studies with larger sample sizes are needed to provide clear evidence on the relationship between PD and OSA, and how their underlying pathophysiologies and pathologies interact with each other.

Conflicts of Interest

None of the authors report any disclosures or conflicts of interest.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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