Comparison of sleep characteristics between Parkinson's disease with and without freezing of gait: A systematic review

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a range of motor and non-motor symptoms. Among the motor complaints, freezing of gait (FOG) is a common and disabling phenomenon that episodically hinders patients' ability to produce efficient steps. Concurrently, sleep disorders are prevalent in PD and significantly impact the quality of life of affected individuals. Numerous studies have suggested a bidirectional relationship between FOG and sleep disorders. Therefore, our objective was to systematically review the literature and compare sleep outcomes in PD patients with FOG (PD + FOG) and those without FOG (PD-FOG). By conducting a comprehensive search of the PubMed and Web of Science databases, we identified 20 eligible studies for inclusion in our analysis. Our review revealed that compared to PD-FOG, PD + FOG patients exhibited more severe symptoms of rapid eye movement sleep behavior disorder in nine studies, increased daytime sleepiness in eight studies, decreased sleep quality in four studies, and more frequent and severe sleep disturbances in four studies. These findings indicate that PD + FOG patients generally experience worse sleep quality, higher levels of daytime sleepiness, and more disruptive sleep disturbances compared to those without FOG (PD-FOG). The association between sleep disturbances and FOG highlights the importance of evaluating and monitoring these symptoms in PD patients and open the possibility for future studies to assess the impact of managing sleep disturbances on the severity and occurrence of FOG, and vice versa.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder [1], characterized by motor and non-motor symptoms [2] making it a leading cause of disability worldwide [3]. Classical motor symptoms such as bradykinesia, resting tremor, and muscular rigidity, form the hallmark features of PD [4]. Additionally, patients may experience postural instability and gait disturbances [5], including freezing of gait (FOG), which significantly impacts their quality of life [6]. FOG defined, as "a brief episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [7] can lead to falls [8], injuries [9], poor quality of life [9] and limited mobility and functional independence [10].

It is a disabling symptom, affecting a significant proportion of PD patients, with a prevalence ranging from 40 to 70 % [11]. FOG episodes can occur under various walking conditions, with common triggers being the initiation of gait, turning, approaching obstacles, navigating through narrow spaces, and performing dual-tasking while walking [10–15]. FOG has been linked to various factors, including longer disease duration, advanced age, higher disease stage, balance difficulties, impaired posture and gait, motor fluctuations, and poor quality of life [11,16–23].

The management of FOG encompasses various treatment approaches, including pharmacological therapies, surgical options, and

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non-pharmacological therapies like physiotherapy and occupational therapy [24]. However, despite these efforts, strategies still remain limited and insufficient, and the available evidence is often inadequate [25]. This limitation is primarily attributed to the poorly understood pathophysiology of FOG [26].

In addition to motor symptoms, PD can also manifest various non-motor symptoms, including autonomic dysfunction, mood alterations, cognitive decline, and sleep disorders [27]. Among these non-motor manifestations, sleep disorders are particularly prevalent, affecting a substantial proportion of PD patients, with prevalence ranging from 40 % to 90 % [28]. These sleep disturbances significantly impact the quality of life of individuals living with PD [28].

Many PD patients commonly report experiencing excessive daytime sleepiness, difficulties with falling or staying asleep, and a specific sleep disorder known as rapid eye movement (REM) sleep behavior disorder (RBD) [29]. RBD is a parasomnia characterized by vivid, violent, and unpleasant dream enactments, often leading to potentially harmful movements during sleep [30]. The bed-partners of PD individuals frequently observe abnormal movements and vocalizations during RBD episodes, such as falling out of bed, limb shaking, violent behaviours, shouting, talking, or even making threats [31].

On the other hand, REM sleep without atonia (RSWA), identified through increased phasic or tonic muscle activity in polysomnographic electromyography during REM sleep, is a diagnostic feature of RBD [32]. RBD has been recognized as a risk factor for the development of α-synucleinopathies, including PD [33]. Remarkably, RBD may precede the onset of motor symptoms in PD by several years and has been considered one of the most relevant prodromal symptoms [34].

Poor sleep quality contributes significantly to the overall burden of PD [27] and has also been associated with poor quality of life, symptoms of depression and anxiety, and pain in PD patients [28,35]. Therefore, the diagnosis and management of sleep disorders in PD patients hold paramount importance [36].

Previous research has highlighted an association between sleep disturbances and FOG in PD [37]. This relationship is evident in terms of both symptom severity and occurrence, with patients experiencing FOG being more likely to report sleep alterations [26,38,39]. Similarly, patients with sleep disturbances, have shown an increased likelihood of developing FOG throughout the disease course [26,40]. The bidirectional association between sleep disturbances and FOG suggests a partial overlap in the underlying pathological mechanisms of these two phenomena [41].

Despite the availability of evidence on this topic, there has been no systematic review to date that directly compares sleep outcomes between PD patients with and without FOG (PD + FOG and PD-FOG). To address this knowledge gap, the present systematic review was specifically designed to explore and compare sleep-related findings in PD patients with and without FOG, aiming to provide valuable insights into the complex interplay between sleep disturbances and FOG in PD.

2. Methods

2.1. Protocol and registration

This systematic review's protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42021274764). The review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [42] and the Cochrane Handbook for Systematic Reviews guidelines [43]. As this review was limited to publicly available materials, it did not require any ethical approval.

2.2. Eligibility criteria

This review included original articles published in English, French or German in peer-reviewed scientific journals. Cross-sectional studies,

longitudinal studies and retrospective studies were included. Case reports, abstracts, editorials, letters to the editor, case studies, reviews, or meta-analyses were excluded. Studies involving patients with a diagnosis of PD were included. The patients had to be aged of 18 years old or older. Studies including animal models or mixed syndromes were excluded. Participants were not required to undergo any type of intervention. Accordingly, studies reporting any measure of sleep and FOG in individuals with PD were included. Therefore, studies not evaluating sleep outcomes in PD + FOG compared with PD-FOG were excluded from this review.

2.3. Data sources and search strategy

The following two electronic databases, PubMed and Web of Science, were systematically searched. No limitation was placed on the date of the publication with databases screened up to February 21, 2023. Keywords related to (1) the population, (2) freezing of gait, and (3) sleep were used. The search strategy included a combination of keywords, using the Boolean operator "AND" and "OR" and, if it was applicable, the Medical Subject Headings (MeSH) terms. The first category of keywords focused the search on patients with PD and included terms such as "Parkinson Disease", "Parkinson's disease", "Parkinson", or "PD". The second category specified FOG. It comprised all following terms: "freezing of gait", "fog", or "frozen gait". The third category was designed to focus on sleep disorders: "sleep", "insomnia", or "dyssomnia". These three categories were combined as follows for the final search: (1) AND (2) AND (3). The search fields were restricted to the abstract, title, and keywords.

2.4. Study selection

Two independent reviewers (TM and MBC) screened the titles, abstracts, and keywords of all the studies found in the search to identify potentially relevant articles. Duplicates were manually removed. After this initial selection, the full-length text articles selected were independently screened for eligibility according to the criteria mentioned above by two reviewers (TM and MBC). In cases of disagreement and if subsequent discussions between the two reviewers were inconclusive, a third reviewer (NV) was contacted to arbitrate the disagreement. In line with the PRISMA guidelines [42], the number of citations reviewed at each stage of the review were summarized in a flow chart (Fig. 1).

2.5. Data extraction

After completion of the screening process, two reviewers (TM and MBC) independently extracted the data from each included study and competed the data for consistency. Any discrepancies between these two reviewers were resolved at a consensus meeting. If disagreement persisted, a third reviewer (NV) was consulted to reach a final decision. Data extraction was done following a prebuilt table including information about study metrics, population, main measures of sleep and FOG in patients with PD. Study metrics referred to the name of authors, title, year of publication, journal's name, country of study, study design, number of centers taking part in the study, funding, and conflicts of interest. Based on a recent published systematic review and meta-analysis on spatiotemporal data and lower limb angles during walking in PD and control populations, only data concerning PD + FOG compared with PD-FOG groups were extracted [44]. Population-related information included sample size, age, gender, weight, height, body mass index, disease qualification, disease duration and severity, occupational status and education. Conclusions and clinical or research implications were also extracted. In case of missing or erroneous data, the study authors were contacted for further information.
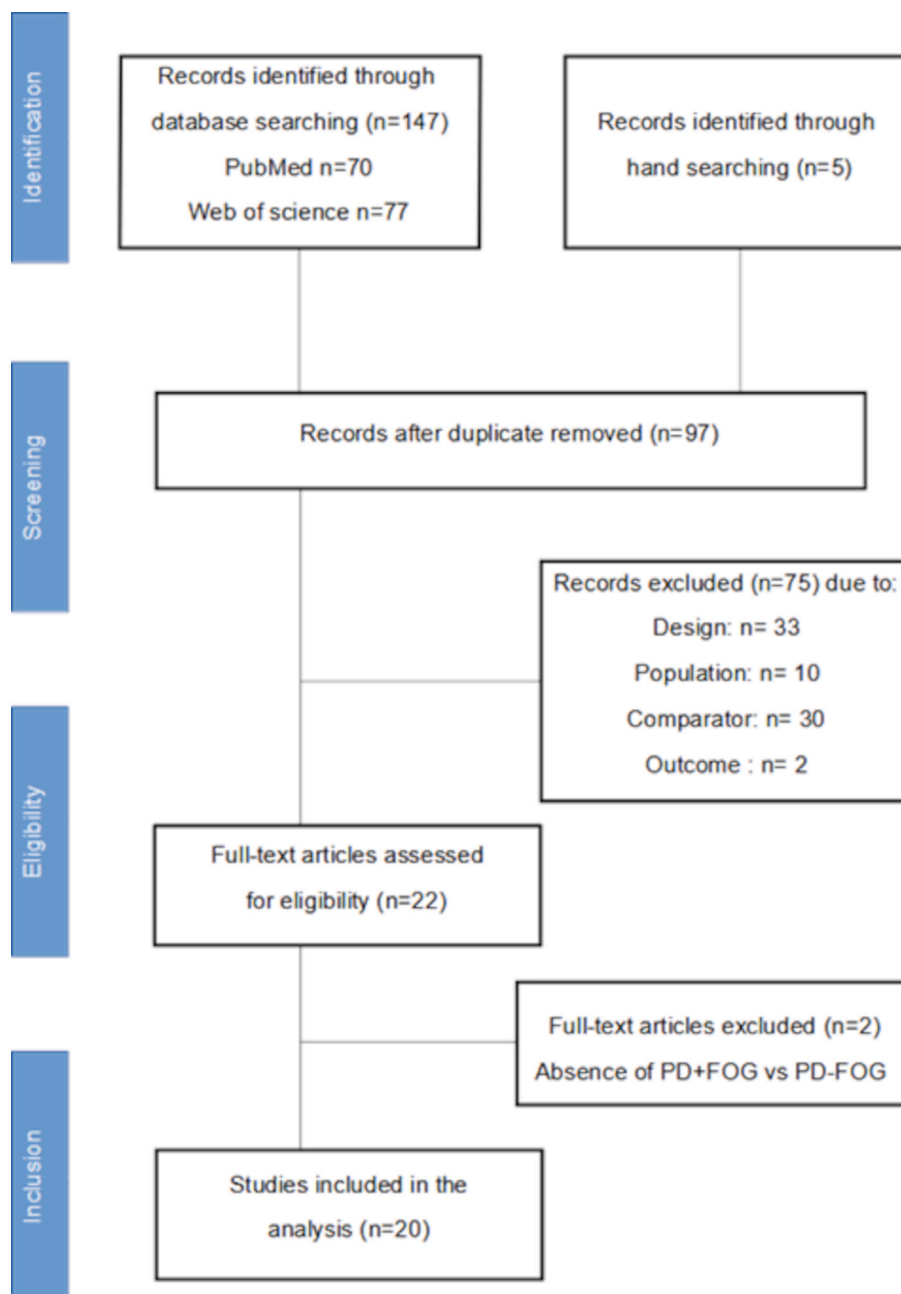
Fig. 1. Flowchart of the selection process.

2.6. Methodological quality

Two review authors (TM and MBC) independently assessed the risk of bias of the included studies. Disagreements between the review authors over the risk of bias for particular studies were resolved by discussion, with the involvement of a third reviewer (NV) who was contacted to arbitrate the disagreement when necessary. The quality assessment of the included studies was conducted using a customized quality checklist recently developed by Zanardi et al. [44] based on initial works from Downs and Black [45]. This instrument was initially intended to assess methodological quality of randomized and non-randomized intervention studies. Only observational studies were included in this study; thus, some items were removed since they were irrelevant to these types of studies (Supplementary File S1).

3. Results

3.1. Study selection

The study selection process is depicted in Fig. 1. Initially, 147 records were identified through database searching, with 70 studies found through PubMed and 77 through Web of Science. An additional five studies were identified through manual hand searching. After removing duplicates (n = 55), a total of 97 unique records remained. Subsequently, these records were screened based on their titles and abstracts, leading to 22 full-text studies being reviewed for eligibility. Ultimately, 20 studies met the eligibility criteria and were included in this systematic review [13,15,20,21,26,37–40,46–56].

3.2. Methodological quality

Among the 20 studies included in this systematic review, all of them clearly described their hypothesis/aim/objective (100 %), primary outcomes (100 %), and principal confounders (100 %). Additionally, all studies reported their main findings (100 %) and demonstrated random variability in the data (100 %). In 85 % of the studies, the characteristics of the participants were clearly mentioned, and 90 % of the studies ensured that the participants were representative of the population. Moreover, 100 % of the studies employed appropriate statistical measurements and accurate methods to assess the main outcome. Probability values were described in 90 % of the studies. Furthermore, 60 % of the studies recruited participants from the same population, and 55 % of them recruited participants from the groups in the same period (Table 1).

3.3. Studies characteristics

Table 2 and Figs. 2 and 3 provide a comprehensive summary of the characteristics of the included studies, encompassing details related to study design, publication year, journal and country of publication, as well as information regarding any potential conflicts of interest and funding sources.

3.4. Sample characteristics

Information regarding the participants included in the studies is provided in Table 3. The collective data from the 20 studies encompassed a total of 5212 PD patients, with 2660 (51 %) of them being male. The mean sample size across the studies was n = 261 (±246), with sample sizes ranging from 20 [40] to 967 [56].

The diagnosis of idiopathic PD was based on the United Kingdom Brain Bank clinical criteria [57] and confirmed by a trained neurologist or a movement disorders specialist in 17 studies (85 %) [13,15,20,21,26, 37,40,46–49,51–56].

PD was diagnosed based on the presence of bradykinesia in one study (5 %) [38] and two studies (10 %) [39,50] did not report how PD was diagnosed. All included studies (n = 20, 100 %) classified PD patients according to the absence or the presence of FOG [13,15,20,21,26,37–40, 46–56] either at baseline (n = 14, 70 %) [13,15,20,26,37,39,40,46–48, 51–53,55];, or at follow up (n = 6, 30 %) [21,38,49,50,54,56].

Among the 20 studies, a total of 3049 (58 %) PD patients with FOG

(PD-FOG) were included. The mean sample size for this group was n = 152 (±172), with sample sizes ranging from 10 [40] to 712 [56]. Additionally, a total of 2163 (42 %) PD patients with FOG (PD + FOG) were examined in the studies. The mean sample size for this group was n = 108 (±95), ranging from 10 [40] to 255 [56].

3.5. FOG assessment methods

In total, five methods have been used to assess FOG in PD patients. The FOG Questionnaire (FOG-Q) [58] was used in 9 studies (45 %) [13, 20,21,47,48,51–54]; including a total of 2924 participants, 1599 PD-FOG (55 %) and 1325 PD + FOG (45 %). FOG-Q consists of 6 items. Two items refer to general gait difficulties and four items concern FOG severity with scores ranging from 0 to 4. FOG was determined if patients have a score ≥1 on item 3 ("Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?").

The New FOG Questionnaire (NFOG-Q) [59] was used in 8 studies (40 %) [15,26,37,40,46,49,55,56] including a total of 1612 participants, 1028 PD-FOG (64 %) and 584 PD + FOG (36 %). In NFOG-Q, one initial item was added to allow detecting FOG and excluding patients who did not experience FOG from the actual scoring of severity in the other parts of the questionnaire. Also, a video was presented to help in demonstrating different types of FOG. FOG presence was confirmed if patients had a score >1 on item 3 ("how frequently do you experience freezing episodes during turning?") [37,40,46] or answer affirmatively on item 1 ("do you experience FOG?") [26,37] or had a score >1 on item 5 ("How frequently do you experience episodes of freezing when initiating the first step?") [37] or, finally, if they had a score ≥1 on NFOG-Q total score [15,49,55,56].

The Unified Parkinson's Disease Rating Scale (UPDRS) [60] was used in one study (5 %) [56] including a total of 967 participants, 712 PD-FOG (74 %) and 255 PD + FOG (26 %). FOG was assessed if patients had a score ≥1 on the item 14 "freezing when walking" with a score ranging from 0 (none) to 4 (frequent falls from freezing).

The Movement Disorder Society (MDS)-UPDRS part II (motor experiences of daily living) [61] was used in four studies (20 %) [39,50,52] including a total of 1394 participants, 777 PD-FOG (56 %) and 617 PD + FOG (44 %). FOG was evaluated based on the item 13 (Freezing: "Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor?") with a score ranging from 0 (normal) to 4 (severe).

Table 1
Quality assessment of included studies based on selected items of a customized quality checklist recently developed by Zanardi and colleagues [44].

Study	Quality Index item Number													Total
	1	2	3	5	6	7	10	11	12	18	20	21	22	
[40]	1	1	1	2	1	1	1	1	1	1	1	0	0	12
[48]	1	1	1	2	1	1	1	1	1	1	1	1	1	14
[20]	1	1	1	2	1	1	1	0	0	1	1	1	1	12
[13]	1	1	1	2	1	1	1	1	1	1	1	1	1	14
[46]	1	1	1	2	1	1	1	1	1	1	1	0	0	12
[21]	1	1	1	2	1	1	1	0	0	1	1	1	1	12
[47]	1	1	1	2	1	1	1	1	1	1	1	1	1	14
[54]	1	1	1	2	1	1	1	1	1	1	1	1	1	14
[39]	1	1	0	2	1	1	1	1	1	1	1	0	0	11
[49]	1	1	1	2	1	1	1	1	1	1	1	0	0	12
[50]	1	1	1	2	1	1	1	1	1	1	1	0	1	13
[55]	1	1	1	2	1	1	0	0	0	1	1	1	1	11
[37]	1	1	1	2	1	1	0	1	1	1	1	0	0	11
[26]	1	1	1	2	1	1	1	1	1	1	1	1	1	14
[56]	1	1	1	2	1	1	1	1	1	1	1	1	1	14
[15]	1	1	1	2	1	1	1	1	1	1	1	1	0	13
[51]	1	1	0	2	1	1	1	0	0	1	1	1	1	11
[52]	1	1	1	2	1	1	1	1	1	1	1	0	0	12
[53]	1	1	0	2	1	1	1	1	1	1	1	1	0	12
[38]	1	1	1	2	1	1	1	0	0	1	1	0	0	10
%	100	100	85	100	100	100	90	75	75	100	100	60	55	

Table 2
Included studies in chronological order of publication.

First author	Publication year	Country	Title	Journal	Funding source	Conflict of interest	Number of centers	Study design
Videnovic et al.	2013	USA	Increased REM sleep without atonia in Parkinson disease with freezing of gait	American Academy of Neurology	Michael J. Fox Foundation for Parkinson's Research	Not mentioned	Not mentioned	Cross-sectional study
Hall et al.	2014	Australia	Early phenotypic differences between Parkinson's disease patients with and without freezing of gait	Parkinsonism and Related Disorders	Not mentioned	Not mentioned	1	Cross-sectional study
Ou et al.	2014	China	Freezing of gait in Chinese patients with Parkinson Disease	Journal of the Neurological Sciences	Not mentioned	None	1	Cross-sectional study
Hall et al.	2015	Australia	Freezing of Gait and its Associations in the Early and Advanced Clinical Motor Stages of Parkinson's Disease: A Cross-Sectional Study	Journal of Parkinson's Disease	Not mentioned	None	1	Cross-Sectional Study
Alibiglou et al.	2016	USA	Subliminal gait initiation deficits in rapid eye movement sleep behavior disorder: A harbinger of freezing of gait?	Movement Disorders	Michael J. Fox Foundation for Parkinson's Research	None	Not mentioned	Cross-sectional study
Zhang et al.	2016	China	A prospective study of freezing of gait with early Parkinson disease in Chinese patients	Medicine	Not mentioned	None	1	Prospective Longitudinal study
Ehgoetz Martens et al.	2018	Australia	Predicting the Onset of Freezing of Gait: A Longitudinal Study	Movement disorders	Funding to Forefront, a collaborative research group dedicated to the study of non-Alzheimer's disease degenerative dementias from the National Health and Medical Research Council of Australia program	None	1	Longitudinal Study
Ou et al.	2018	China	Predictors of freezing of gait in Chinese patients with Parkinson's disease	Brain and Behavior	National Science Fund of China and National Key Research and Development Program of China	None	1	Longitudinal study
Banks et al.	2019	USA	Non-motor predictors of freezing of gait in Parkinson's disease	Gait Posture	National Institute of General Medical Sciences	None	Not mentioned	Longitudinal study
Herman et al.	2019	Israel	Depressive symptoms may increase the risk of the future development of freezing of gait in patients with Parkinson's disease: Findings from a 5-year prospective study	Parkinsonism and Related Disorders	The Michael J. Fox Foundation for Parkinson's Research.	None	Not mentioned	Longitudinal Study
Kim et al.	2019	South Korea	CSF β-amyloid42 and risk of freezing of gait in early Parkinson disease	American Academy of Neurology	Seoul National University Hospital Research Fund and Seoul National University College of Medicine Research Foundation	None	Multi-center	Longitudinal study
Sawada et al.	2019	Japan	Clinical features of freezing of gait in Parkinson's disease patients	Brain and Behavior	Japan Society for the Promotion of Science	None	1	Cross-sectional study
de Almeida et al.	2021	Brazil	Poor sleep quality is associated with cognitive, mobility, and anxiety disability that underlie freezing of gait in Parkinson's disease	Gait Posture	Fundaçao de Amparo à Pesquisa do Estado de Sao Paulo, Conselho Nacional de Desenvolvimento Científico e Tecnologico National Institutes of Health, and Department of Veterans Affairs Merit Award	None	2	Cross-sectional study
Tang et al.	2021	China	Association of sleep disturbance and freezing of gait in Parkinson disease: prevention/delay implications	The Journal of Clinical Sleep Medicine	The Projects of the National Natural Science Foundation of China the Project of Shanghai Municipal Education Commission of China; the Project of Shanghai Municipal Health and Family Planning Commission of China, the Project of Shanghai Jiao Tong University of China; the Project of National Eastern Tech-	None	1	Longitudinal prospective study

Table 2 (*continued*)

| First author	Publication year	Country	Title	Journal	Funding source	Conflict of interest	Number of centers	Study design
					transfer Center; the Projects of Shanghai Committee of Science and Technology; National Key R&D Program of China; SHSMU-ION Research Center for Brain Disorders.			
Xu et al.	2021	China	Constructing Prediction Models for Freezing of Gait by Nomogram and Machine Learning: A Longitudinal Study	Frontiers in Neurology	The National Key Research and Development Program of China	None	1	Longitudinal Study
Zhang et al.	2021	China	Clinical features and related factors of freezing of gait in patients with Parkinson's disease	Brain and Behavior	National Science Foundation of China, the Key R & D Plan Project of Ningxia, Overseas Students' Innovation and Entrepreneurship Individual Project of Ningxia Province, Young Talent Grant of Ningxia Medical University	None	1	Cross-sectional study
Landes et al.	2022	USA	Levodopa ONOFF-state freezing of gait: Defining the gait and non-motor phenotype	PLOS One	The University of Arkansas Clinician Scientist Program, NIGMS P30 award and the Parkinson's Foundation	None	1	Cross-sectional study
Li et al.	2022	China	Development and validation of a nomogram for freezing of gait in patients with Parkinson's Disease	Acta Neurologica Scandinavia	Yunnan Province Clinical Research Center for Neurological Diseases, National Natural Science Foundation of China, Scientific Research Fund project of Yunnan Education Department	None	Multi-center	Retrospective study
Lv et al.	2022	China	Associated factors and abnormal dorsal raphe nucleus connectivity patterns of freezing of gait in Parkinson's disease	Journal of Neurology	National Natural Science Foundation of China	None	1	Cross-sectional study
Wang et al.	2022	China	Predicting the onset of freezing of gait in Parkinson's disease	BMC neurology	Shanghai Pujiang Program, Medical and Engineering Cross Research Fund from Shanghai Jiao Tong University, Shanghai Municipal Health Commission Clinical Study Special Fund, Ruijin Hospital Guangci Excellence Youth Training Program; Ruijin Youth NSFC Cultivation Fund.	None	Multi-center	Longitudinal study
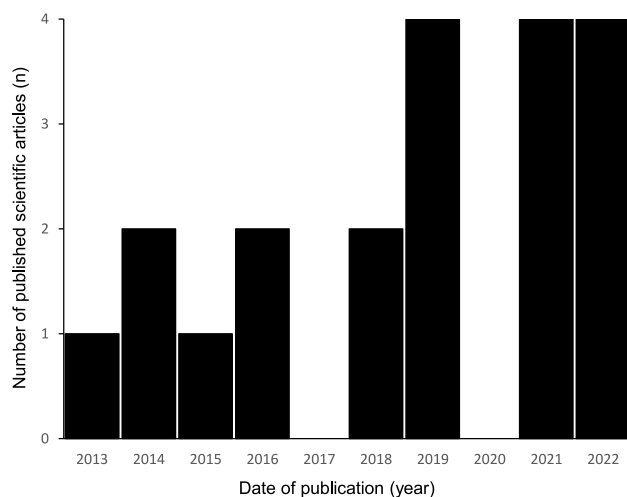
Fig. 2. Number of included articles published per year.

Clinical observation of FOG in addition to the previous cited subjective scales was also used in 13 studies (65 %) [13,20,21,26,37,38,46,49,50,52,54–56] including a total of 4145 participants, 2366 PD-FOG (57 %) and 1779 PD + FOG (43 %). In one study, FOG was evaluated based on the MDS-UPDRS part III item 11 which allows clinical recording of FOG severity [62] with a score ranging from 0 (normal) to 4 (severe) [61]. Again, individuals with PD were instructed to walk naturally in a fixed course after creating some situations that lead to FOG occurrence and FOG was checked at 5 points (hesitation at gait initiation, straight gait, hesitation through a narrow space, hesitation when turning, hesitation at the destination approach) [55]. Also, a movement disorders specialist used videos of some objective tests practiced by PD patients (obstacle-crossing, walking through a doorway, turning clockwise/counterclockwise) [37]. FOG was confirmed as well when patients were asked to turn in place several times to the right and left direction in case of doubt in the presence of FOG [26].

FOG assessment methods are illustrated in supplementary File S2.

3.6. Comparison of sleep outcomes in PD patients with and without FOG

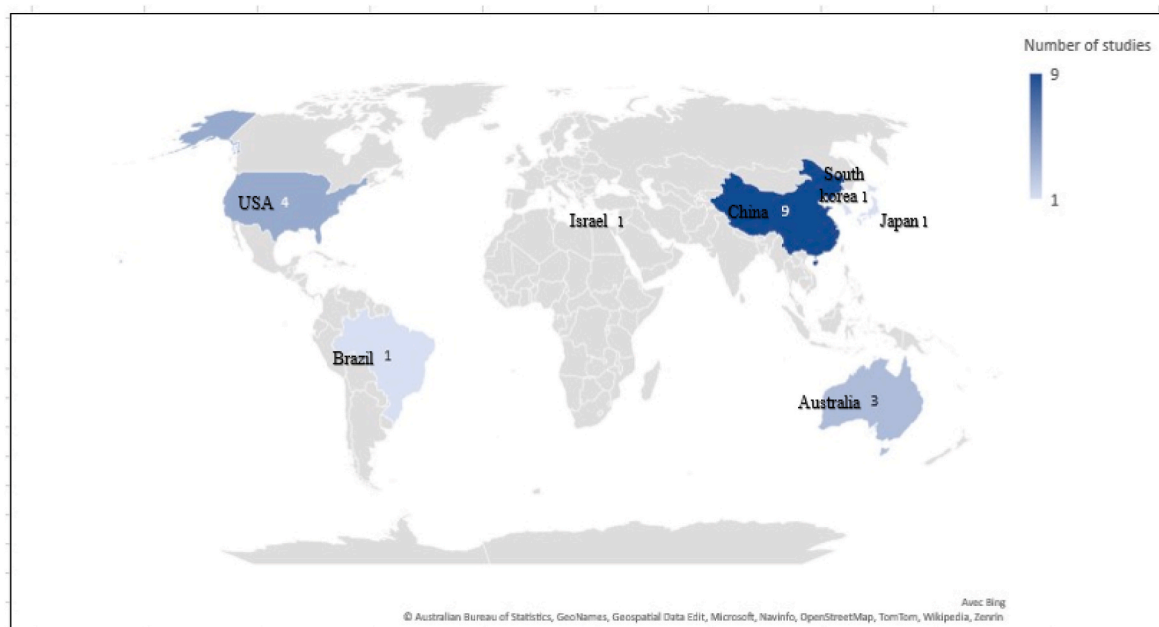The included studies reported various sleep outcomes including.

Fig. 3. World map showing the distribution of the number of published articles by world countries.

- RBD (RBD Screening Questionnaire (RBDSQ), RBDSQ4, RBD Questionnaire-Hong Kong (RBDQ-HK), polysomnography) in 15 studies (75 %) [13,15,26,38–40,46–48,50–53,55,56]
- daytime sleepiness (Epworth Sleepiness Scale (ESS), Japanese version of ESS (JESS)) in ten studies (50 %) [15,26,38–40,50,51,53,55,56]
- sleep quality (Pittsburgh Sleep Quality Index (PSQI)) in six studies (30 %) [26,37,40,49,52,55]
- sleep disturbances (Parkinson's Disease Sleep Scale (PDSS), Hamilton Depression Rating Scale (HAMD), Non Motor Symptoms Scale (NMSS)) in (6 studies (30 %) [20,21,26,53,54,56]

Table 4 presents a detailed compilation of sleep parameters utilized to compare sleep outcomes between PD + FOG and PD-FOG groups. The assessment of sleep in PD patients involved a total of ten distinct methods. Further elaboration and descriptions of these sleep assessment methods can be found in supplementary File S2 and S3.

3.6.1. Analysis of RBD

RBD was assessed in 15 studies (75 %) [46]; [13,15,26,38–40,47,48,50–53,55,56], including a total of 4129 participants (79 %), 2466 PD-FOG (60 %) and 1663 PD + FOG (40 %).

The RBDSQ [63] was reported in nine studies (45 %) [13,15,38,39,48,50–52,55], including a total of 2285 participants (44 %), 1148 PD-FOG (50 %) and 1137 PD + FOG (50 %). RBDSQ is a 13-item scale with a yes or no response to short questions and a maximum score of 13 with higher score being more severe. RBDSQ scores were significantly higher in PD + FOG compared with PD-FOG in 5 studies [13,39,50,52,55]. RBDSQ scores were dependent on the PD disease severity. RBDSQ scores were significantly higher by a median of 2.0 in PD + FOG group compared with PD-FOG group in early stages of the disease, while no significant differences were found in advanced stages between both PD groups [13]. RBDSQ scores were higher by 0.5 (12.5 %) in PD + FOG than PD-FOG [50]. RBDSQ scores were related as well on the method of evaluation of FOG. RBDSQ scores were increased by a median of 1.0 in the PD + FOG group in which FOG was clinically determined compared with PD-FOG [55], while there was no significant difference between the PD + FOG group in which FOG was self-reported and PD-FOG [55].

RBDSQ scores increased significantly in PD + FOG compared with PD-FOG by 3.04 (45.1 %) at the fourth year of follow-up, while the

scores at baseline were not different between PD groups (5.42 ± 3.20 vs 4.24 ± 2.76, respectively) [39]. In one study (5 %), in both validation and training cohorts, the scores were higher in PD + FOG compared with PD-FOG by 1.12 (34 %) and 0.83 (33 %) respectively [52]. Four studies (20 %) did not show any significant difference in RBDSQ scores between PD + FOG and PD-FOG ([15,38,48,48,51]: PD + FOG: 5.11 ± 3.69 vs PD-FOG: 4.87 ± 3.22 [15];: PD + FOG: 30.03 ± 24.39 vs PD-FOG: 28.53 ± 28.47 [51];: PD + OFF-FOG (PD with levodopa responsive FOG): 5.9 (4.9, 6.9) vs PD + ONOFF-FOG (PD with levodopa-unresponsive FOG): 5.2 (3.9, 6.4) vs PD-FOG: 5.0 (4.0, 5.9) [38];: PD + FOG: 3.00 (2.00; 5.00) vs PD-FOG: 3.00 (2.00; 5.50)].

The RBDSQ4 [64] was utilized in two studies (10 %) [47,48], encompassing a total of 312 participants (6 %), with 141 PD-FOG (45 %) and 171 PD + FOG (55 %). The RBDSQ4 assesses questions 4 to 7 of the RBDSQ, and interestingly, both studies [47,48] reported contradictory results concerning its findings. Hall and colleagues did not report any significant difference in RBDSQ4 scores between PD + FOG (n = 38) and PD-FOG (n = 53) [48] (2.33 ± 2.40 vs 1.94 ± 2.32, respectively). Conversely, Ehgoetz Martens and collaborators observed that RBDSQ4 scores were significantly higher by 1.05 (64 %) and 0.79 (43 %), respectively at baseline and follow up assessment in the continuing PD + FOG group, who reported ≥1 at baseline and follow up on the item 3 of FOG-Q, compared with PD-FOG [47]. Whereas, in the same study, RBDSQ4 scores in the transitional PD + FOG group, who reported 0 at baseline and ≥1 at follow up on the item 3 of FOG-Q, were not different from the continuing PD + FOG group and PD-FOG group [47].

The RBDQ-HK [65] was utilized in three studies (15 %) [26,53,56], comprising a total of 1583 participants (30 %), with 1210 PD-FOG (76 %) and 373 PD + FOG (24 %). This 13-item questionnaire assesses a score range from 0 to 100, with higher scores indicating more severe symptoms. However, the RBDQ-HK scores yielded contrasting results across the studies. On the one hand, Tang et al. did not report any significant difference in the proportion of PD patients with RBD between PD + FOG (n = 64) and PD-FOG (n = 99) groups (44 % vs 48 %, respectively) [26]. On the other hand, two studies ([53]; Xu et al., 2022) recently reported a higher proportion of PD patients with RBD in PD + FOG group than PD-FOG group ([56]: n = 255, 42.35 % vs n = 712, 30.9 % & Lv et al., 2022: n = 453, 40.7 % vs 26.6 % respectively) [56]. However, after adjusted analysis in Lv et al. study [53], there were no significant difference in RBD between the two groups.

Table 3
Main characteristics of included studies.

Study	Year	Main objective	FOG assessment method	Medication status (during FOG assessment)	Sleep assessment method	Medication status (during sleep assessment)	PD + FOG characteristics	PD-FOG characteristics	Length of follow up
Videnovic et al.	2013	To compare muscle activity during REM sleep between patients with and without FOG, patients with RBD, and age-matched controls.	NFOG-Q	NM	RBD: PSG Daytime sleepiness: ESS Sleep quality: PSQI	NM	n = 10, 8 M Age: 65.9 ± 11.2 y PD duration: 7.2 ± 4.1 y H&Y: 2.2 ± 0.3	n = 10, 8 M Age: 61.5 ± 9.4 y PD duration: 4.4 ± 2.5 y H&Y: 2.0 ± 0.2	NA
Hall et al.	2014	To identify phenotypic differences between patients with and without freezing in the early clinical stages of PD, matching groups for age, disease duration and severity, and medication.	FOG-Q	NM	RBD: RBDSQ RBDSQ4	NM	n = 38, 27 M Age: 65.2 ± 9.0 y PD duration: 1.91 ± 1.40 y H&Y: 2.00 ± 0.42	n = 53, 35 M Age: 64.58 ± 8.63 y PD duration: 1.69 ± 1.26 y H&Y: 1.85 ± 0.44	NA
Ou et al.	2014	To explore the prevalence and clinical correlates of FOG in a large cohort of Chinese PD patients.	FOG-Q Clinical	NM	Sleep disturbances: NMSS	ON	n = 221 Age: 64.36 ± 10.16 y PD duration: 5.97 ± 4.24 y H&Y: 2.5 ± 1.0	n = 253 Age: 60.11 ± 10.50 y PD duration: 3.73 ± 3.55 y H&Y: 2.0 ± 0.5	NA
Hall et al.	2015	To investigate the prevalence of freezing of gait and its associations with increasing disease severity to gain a better understanding of the underlying pathophysiology.	FOG-Q Clinical (MDS-UPDRS III)	ON	RBD: RBDSQ	NM	Early stage: n = 69, 45 M Age: 65.03 (59.61–71.77) y PD duration: 6.21 (3.50–9.44) y H&Y: 2.00 (2.00–2.00) Advanced stage: n = 172, 97 M Age: 75.15 (68.47–80.91) PD duration: 9.95 (4.24–16.62) H&Y: 3.00 (2.63–4.00)	Early stage: n = 113, 75 M Age: 66.47 (61.49–72.32) y PD duration: 3.43 (1.70–6.28) y H&Y: 2.00 (1.00–2.00) Advanced stage: n = 35, 17 M Age: 78.50 (68.64–84.51) PD duration: 4.34 (1.72–7.05) H&Y: 3.00 (2.50–3.00)	NA
Alibiglou et al.	2016	To examine whether individuals with rapid eye movement sleep behavior disorder who do not have a diagnosis of PD show abnormalities in gait initiation that resemble the impairments observed in PD and whether there is a relationship between these deficits and the level of rapid eye movement sleep without atonia.	NFOG-Q Clinical	NM	RBD: PSG	NM	n = 10, 8 M Age: 65.9 ± 11.2 y PD duration: 7.2 ± 4.1 y H&Y: 2.2 ± 0.3	n = 10, 8 M Age: 61.5 ± 9.4 y PD duration: 4.4 ± 2.5 y H&Y: 2.0 ± 0.2	NA
Zhang et al.	2016	To investigate the risk factors for FOG in the early stage of PD.	FOG-Q Clinical	NM	Sleep disturbance: HAMD NMSS	NM	n = 128, 55 M Age: <65 y: n = 18, ≥65 y: n = 110 PD duration: NM H&Y: NM	n = 120, 57 M Age: <65 y: n = 60, ≥65 y: n = 60 PD duration: NM H&Y: NM	3 years
Ehgoetz Martens et al.	2018	To examine longitudinal data spanning the transition period when patients with PD developed freezing of gait to identify symptoms that may precede freezing and create a prediction model that identifies those "at risk" for developing freezing of gait in the year to follow".	FOG-Q	NM	RBD: RBDSQ4	NM	Transitional: n = 41, 26 M Age: 70.75 ± 9.39 y PD duration: 5.97 ± 4.14 y H&Y: NM Continuing: n = 92, 56 M Age: 70.24 ± 10.85 y PD duration: 9.66 ± 7.50 y H&Y: NM	n = 88, 52 M Age: 65.37 ± 9.84 y PD duration: 3.16 ± 4.32 y H&Y: NM	1 year

Table 3 (*continued*)

Study	Year	Main objective	FOG assessment method	Medication status (during FOG assessment)	Sleep assessment method	Medication status (during sleep assessment)	PD + FOG characteristics	PD-FOG characteristics	Length of follow up
Ou et al.	2018	To explore the clinical predictors of freezing of gait (FOG) in Chinese patients with Parkinson's disease (PD).	FOG-Q Clinical	Did not differentiate between ON and OFF	Sleep disturbances: NMSS	OFF	n = 85, 44 M Age: 62.5 ± 11.1 y PD duration: 6.8 ± 3.3 y H&Y: Baseline: 2.4 ± 0.6 Follow-up: 2.9 ± 0.8	n = 140, 85 M Age: 58.1 ± 12.6 y PD duration: 4.5 ± 2.4 y H&Y: Baseline: 1.5 ± 0.6 Follow-up: 2.2 ± 0.5	3 years
Banks et al.	2019	To determine which cognitive and/or non-cognitive deficits can be used as early symptoms to predict FOG onset later in the disease, in the hope that treatment approaches targeting these deficits might prevent FOG development.	MDS-UPDRS II	NM	RBD: RBDSQ Daytime sleepiness: ESS	NM	n = 50, 30 M Age: 60.46 ± 11.61 y PD duration: NM H&Y: NM	n = 50, 38 M Age: 60.74 ± 7.20 y PD duration: NM H&Y: NM	4 years
Herman et al.	2019	To explore which symptoms are associated with future development of FOG in non-freezers.	NFOG-Q Clinical	ON and OFF	Sleep quality: PSQI	NM	n = 26, 20 M Age: 64.8 ± 10.0 PD duration: 4.2 ± 2.3 H&Y: NM	n = 31, 19 M Age: 65.6 ± 9.3 PD duration: 4.5 ± 2.9 H&Y: NM	5 years
Kim et al.	2019	To determine whether CSF biomarkers can be used as a predictor of freezing of gait (FOG) in Parkinson disease (PD) and to investigate the predictive value of clinical, dopamine transporter (DAT) imaging, and CSF parameters both separately and in combination.	UPDRS II Clinical (MDS-UPDRS-III)	ON and OFF	RBD: RBDSQ Daytime sleepiness: ESS	NM	n = 136, 100 M Age: NM PD duration: 1.8 ± 1.4 y H&Y: NM	n = 257, 159 M Age: NM PD duration: 2.0 ± 2.2 y H&Y: NM	4 years
Sawada et al.	2019	To compare the clinical features (such as demographic characteristics, motor symptoms, non-motor symptoms, cognitive function, and medication use) between FOG identified by a clinical examination and FOG identified by a questionnaire.	NFOG-Q Clinical	OFF	RBD: RBDSQ Daytime sleepiness: JESS Sleep quality: PSQI	NM	PD + SFOG: n = 101, 44 M Age: 71.5 (65.3–76.8) y PD duration: 6.0 (2.0–10.0) y H&Y: 3.0 (2.0–3.0) PD + CFOG: n = 41, 18 M Age: 75.0 (69.0–80.0) y PD duration: 10.0 (5.0–15.0) y H&Y: 3.0 (3.0–4.0)	n = 87, 31 M Age: 71.0 (64.0–78.0) y PD duration: 4.0 (2.0–7.0) y H&Y: 2.0 (1.0–3.0)	NA
de Almeida et al.	2021	To determine if poor sleep quality was associated with FOG severity, with all three components of the FOG phenotype (cognitive, anxiety, and mobility), and with disease severity. To verify if FOG, cognition, anxiety, and mobility explained the variance of the PSQI scores in PD + FOG. To compare sleep quality, cognitive function, anxiety, and mobility among PD + FOG, PD-FOG and HC.	NFOG-Q Clinical	ON	Sleep quality: PSQI	ON	n = 40, 29 M Age: 62.3 ± 9.4 y PD duration: 8.8 ± 4.9 y H&Y: 3.2 ± 0.4	n = 39, 29 M Age: 62.7 ± 9.6 y PD duration: 8.7 ± 4.5 y H&Y: 2.5 ± 0.5	NA

Table 3 (*continued*)

Study	Year	Main objective	FOG assessment method	Medication status (during FOG assessment)	Sleep assessment method	Medication status (during sleep assessment)	PD + FOG characteristics	PD-FOG characteristics	Length of follow up
Tang et al.	2021	To investigate the relationship between sleep disturbance and FOG in PD.	NFOG-Q Clinical	ON	RBD: RBDQ-HK Daytime sleepiness: ESS Sleep quality: PSQI Sleep disturbances: PDSS	NM	n = 64, 36 M Age: 68.2 ± 7.7 y PD duration: 6.4 (4.2–9.9) y H&Y: 2.6 ±. 6	n = 99, 53 M Age: 66.4 ± 6.2 PD duration: 4.4 (2.2–7.2) y H&Y: 2.0 ±. 6	NA
Xu et al.	2021	To find out some clinical characteristics in FOG patients, identify some risk factors of FOG, and construct prediction models of FOG.	NFOG-Q UPDRS-14 Clinical	OFF	RBD: RBDQ-HK Daytime sleepiness: ESS Sleep disturbances PDSS	OFF	n = 255, 119 M Age: 62.3 ± 9.4 y PD duration: 7.18 ± 4.02 y H&Y: NM	n = 712, 377 M Age: 62.7 ± 9.6 y PD duration: 5.48 ± 3.37 y H&Y: NM	1 year
Zhang et al.	2021	To explore the clinical characteristics and related factors of FOG in patients with Parkinson's disease.	NFOG-Q	NM	RBD: RBDSQ Daytime sleepiness: ESS	NM	n = 37, 19 M Age: 63.92 ± 10.52 y PD duration: 7.0 (4.0–10.0) y H&Y: 3.18 ± 0.60	n = 40, 21 M Age: 60.83 ± 8.58 y PD duration: 4.5 (2.0–5.0) y H&Y: 2.30 ± 0.62	NA
Landes et al.	2022	To identify an objectively quantifiable feature set from gait, gross-motor and non-motor assessments that distinguish between people with PD that have OFF-FOG, ONOFF-FOG or no FOG phenotypes.	FOG-Q	ON, OFF	RBD: RBDSQ Daytime sleepiness: ESS	ON, OFF	OFF-FOG n = 36, 18 M Age: 64.9 ± 8.6 y PD duration: 9.4 ± 6.4 y H&Y: 2.2 ± 0.5 ONOFF-FOG n = 26, 16 M Age: 70.5 ± 8.1 y PD duration: 10.4 ± 5.1 y H&Y: 3.2 ± 0.9	n = 43, 25 M Age: 67.1 ± 8.2 y PD duration: 6.2 ± 4.9 y H&Y: 1.8 ± 0.5	NA
Li et al.	2022	To develop a nomogram for FOG risk based on data collected from Chinese patients with PD.	UPDRS-II FOG-Q Clinical (MDS-UPDRS-III)	Did not differentiate between ON and OFF	RBD: RBDSQ Sleep quality: PSQI	NM	Training dataset n = 197, 111 M Age: 68.26 ± 10.17 y PD duration: 5.23 ± 4.68 y H&Y: 0: 1; 1: 52; 2: 37; 3: 60, 4: 33; 5: 14 Validation dataset n = 166, 72 M Age: 62.6 ± 10.30 y PD duration: 5.98 ± 5.03 y H&Y[1] : 0: 0; 1: 30; 2: 83; 3: 34, 4: 14; 5: 5	Training dataset n = 182, 112 M Age: 64.20 ± 10.40 y PD duration: 3.47 ± 3.64 y H&Y: 0: 0; 1: 94; 2: 55; 3: 27, 4: 4; 5: 2 Validation dataset n = 173, 89 M Age: 61.23 ± 10.80 y PD duration: 3.35 ± 3.41 y H&Y[1] : 0: 1; 1: 78; 2: 77; 3: 16, 4: 1; 5: 0	NA
Lv et al.	2022	To determine factors associated with FOG in PD patients and to evaluate the importance of the dorsal raphe nucleus in FOG pathophysiology.	FOG-Q	OFF	RBD: RBDQ-HK Sleep disturbances: PDSS Daytime sleepiness: ESS	OFF	n = 54, 25 M Age: 64 (55, 70) y PD duration: 48 (24, 96) months H&Y[2]: 23/31	n = 399, 217 M Age: 59 (52, 66) y PD duration: 24 (12, 48) months H&Y[2]: 357/42	NA

Table 3 (*continued*)

Study	Year	Main objective	FOG assessment method	Medication status (during FOG assessment)	Sleep assessment method	Medication status (during sleep assessment)	PD + FOG characteristics	PD-FOG characteristics	Length of follow up
Wang et al.	2022	To determine the early symptoms and characteristics exhibited in PD patients before FoG occurrence.	MDS-UPDRS II Clinical (MDS-UPDRS III)	Did not distinguish between ON and OFF	RBD: RBDSQ Daytime sleepiness: ESS	NM	n = 68, 49 M Age: 64.9 [56.8; 69.6] y PD duration: 3.87 [2.33; 7.22] months H&Y: Stage 1: 30 (44.1 %) Stage 2: 37 (54.4 %) Stage 3: 1 (1.47 %)	n = 115, 81 M Age: 60.3 [52.8; 68.5] y PD duration: 4.82 [2.46; 7.02] months H&Y: Stage 1: 54 (47.0 %) Stage 2: 61 (53.0 %) Stage 3: 0 (0.00 %)	5 years

Values are mean ± standard deviation or median (interquartile range) or [1]: number of PD in each stage; [2]: number of PD in stage 1–2.5/stage 3–5.

PD + FOG: Parkinson's disease with freezing of gait; PD-FOG: Parkinson's disease without freezing of gait; CFOG: clinically observed FOG; SFOG: self-reported FOG; PD: Parkinson's disease; M: Male; transitional: PD reported 0 at baseline and ≥1 at follow up on the FOG-Q item 3; continuing: PD reported ≥1 at baseline and follow up on the FOG-Q item 3; RBDSQ: REM sleep behavior disorder screening questionnaire; RBDQ-HK: REM sleep behavior disorder questionnaire Hong Kong; ESS: Epworth sleepiness scale; JESS: Epworth sleepiness scale Japanese version; PSQI: Pittsburgh sleep quality index; PDSS: Parkinson's disease sleep scale; NMSS: non-motor symptoms scale; HAMD: Hamilton depression rating scale; H&Y: Hoehn & Yahr stage; ONOFF-FOG: levodopa-unresponsive FOG; OFF-FOG: levodopa responsive FOG; NA: not applicable; NM: not mentioned.

Polysomnography [66] was employed in two studies (10 %) [40,46], involving a total of 40 participants (1 %), with 20 PD-FOG (50 %) and 20 PD + FOG (50 %). These studies utilized EMG recordings, sleep stages assessment, and REM sleep without atonia (RSWA) quantified as the percentage of phasic and tonic REM during overnight sleep.

Tonic RSWA has increased by 20.60 (189 %) in PD + FOG (n = 20) compared with PD-FOG (n = 20) [40,46], while no significant difference was reported in phasic RSWA between PD + FOG and PD-FOG groups (7.1 ± 4.0 vs 3.8 ± 4.0, respectively) [40,46].

Other polysomnographic measures including total sleep time, sleep efficiency and latency, REM sleep latency, and the percentage of sleep during different sleep stages (N1, N2, N3) showed no significant difference between PD + FOG (n = 20) and PD-FOG (n = 20) [40].

3.6.2. Analysis of daytime sleepiness

Daytime sleepiness was assessed in ten studies (50 %) [15,26,38–40, 50,51,53,55,56], encompassing a total of 2690 participants (52 %) with 1772 PD-FOG (66 %) and 918 PD + FOG (34 %).

The ESS [67] was utilized in nine studies (45 %) [15,26,38–40,50,51, 53,56], with a total of 2461 participants (47 %), comprising 1725 PD-FOG (70 %) and 736 PD + FOG (30 %). This tool is employed to assess excessive daytime sleepiness over the past 1–4 weeks. It involves a list of 8 situations where individuals rate their tendency to become sleepy, assigning scores ranging from 0 to 3, where 0 indicates no chance of dozing and 3 indicates a high chance of dozing (ESS ≥10 indicates excessive daytime sleepiness). ESS scores were significantly higher in PD + FOG than PD-FOG in 7 studies (35 %) [15,26,38,39,50,53,56]. ESS scores were significantly greater by 1.0 (19 %) [50], 2.62 (53 %) [39], 3.0 (60 %) [26], 3.49 (47 %) [15] and 1.0 (20 %) [38] in PD + FOG than PD-FOG. Also, ESS scores were significantly higher by 3.04 (45.1 %) in PD + FOG than PD-FOG at follow up assessment [39]. The proportion of PD who presented with excessive daytime sleepiness was significantly higher in PD + FOG compared with PD-FOG ([56]: 40.78 % vs 29.35 % & Wang et al., 2022: 50.0 % vs 27.3 % respectively) [38,56]. In contrast, two studies (10 %) [40,51], found no difference in ESS scores between PD + FOG and PD-FOG. These authors reported that PD patients in PD + FOG and PD-FOG groups did not have excessive daytime sleepiness with an ESS score ≤10 for both groups ([40]: PD + FOG: 7.8 ± 3.7 vs PD-FOG: 8.9 ± 3.9 [51];: PD + OFF-FOG (PD levodopa responsive FOG): 7.8 (6.3, 9.3), PD + ONOFF-FOG (PD levodopa-unresponsive FOG): 9.1 (7.4, 10.9), PD-FOG: 7.6 (6.2, 9.0)).

The JESS [68] was utilized in one study (5 %) [55], comprising a total of 229 participants (4 %), including 87 PD-FOG (38 %) and 142 PD + FOG (62 %). JESS was designed as an adapted version of the original ESS, where two questions (questions 1 and 8) were replaced to suit the Japanese population better, maintaining content equivalence with ESS. Notably, JESS scores in both PD + FOG groups (n = 142), which included participants with clinically reported or self-reported FOG, were significantly higher by a median of 2.0 compared to the PD-FOG group (n = 87).

3.6.3. Analysis of sleep quality

Sleep quality was evaluated in six studies (30 %) [26,37,40,49,52, 55], involving a total of 1266 participants (24 %), with 621 PD-FOG (49 %) and 645 PD + FOG (51 %).

The PSQI [69] was utilized in 6 studies (30 %) [26,37,40,49,52,55], comprising a total of 1266 participants (24 %), with 621 PD-FOG (49 %) and 645 PD + FOG (51 %). This questionnaire is employed to evaluate the quality of sleep in the previous month. It consists of 19 items combined to form 7 component scores, with scores ranging from 0 (no difficulty) to 3 (severe difficulties), where PSQI >5 indicates poor sleepers.

PSQI scores were significantly higher in PD + FOG than PD-FOG in 4 studies [26,37,52,55]. Total PSQI scores were higher by 4.4 (53 %) [37], 2.03 (30 %) and 1.86 (23 %) in both validation and training cohorts, respectively in PD + FOG than PD-FOG groups. Also, total PSQI scores were higher by a median of 2.0 [55] and 4.5 [26] in PD + FOG groups than PD-FOG. Conversely, 2 studies (10 %) [40,49] reported that PSQI scores did not significantly differ between PD + FOG and PD-FOG, where both groups obtained PSQI scores>5.

The PSQI sub scores, reported in three studies (15 %) [26,37] were higher in PD + FOG (n = 104) than PD-FOG (n = 138), except for sleep medication. The scores on PSQI sub items of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance and daytime dysfunction were higher by 0.9 (69 %), 1.0 (77 %), 0.9 (112,5 %), 0.5 (50 %), 0.6 (40 %) and 0.8 (114 %), respectively in PD + FOG than PD-FOG [37]. Scores on sleep quality, sleep latency, sleep duration, and daytime dysfunction were higher by a median of 1.0 in PD + FOG than PD-FOG. Sleep quality, duration and efficiency were significantly reduced in PD + FOG [26,37]. Sleep onset latency, sleep disturbances and daytime dysfunction were significantly increased in PD + FOG [26, 37].

3.6.4. Analysis of sleep disturbances

Sleep disturbances were evaluated in six studies (30 %) ([20,53,54]; Tang et al., [21,56]), involving a total of 2778 participants (53 %), of which 1843 had PD-FOG (66 %) and 935 had PD + FOG (34 %).

Table 4

List and values of sleep parameters used in studies to compare sleep outcomes in PD + FOG and PD-FOG groups.

Sleep parameters	Number of studies	Study	Significance	Results (mean ± SD or Median (IQR)) or direction of difference (↑↓) with absolute value
Rapid eye movement sleep Behavior Disorder				
RBDSQ	9	[48]	NS: p = 0.742	PD + FOG: 5.11 ± 3.69, PD-FOG: 4.87 ± 3.22
		[13]	**p = 0.004**	**↑ (2; 50 %) PD + EFOG: 6.00 (3.25–9.00), PD-EFOG: 4.00 (2.00–7.00)**
			NS: p = 0.031	PD + AFOG: 6.00 (3.00–9.00), PD-AFOG: 4.00 (2.00–6.50)
		[50]	**p = 0.043**	**↑ (0.5; 12.5 %) PD + FOG: 4.5 ± 2.7, PD-FOG: 4.0 ± 2.5**
		[55]	NS: p > 0.05	PD + SFOG: 3.0 (2.0–6.0), PD-FOG: 3.0 (1.0–5.0)
			p < 0.05	**↑ (1; 33 %) PD + CFOG: 4.0 (2.0–7.0), PD-FOG: 3.0 (1.0–5.0)**
		[39]	NS: p > 0.05	Baseline: PD + FOG: 5.42 ± 3.20, PD-FOG: 4.24 ± 2.76
			p = 0.022	**↑ (1.74; 40 %) Year 4: PD + FOG: 6.12 ± 3.19, PD-FOG: 4.38 ± 2.96**
		[15]	NS: p = 0.805	PD + FOG: 30.03 ± 24.39, PD-FOG: 28.53 ± 28.47
		[51]	NS: p = 0.363	PD + OFF-FOG: 5.9 (4.9, 6.9), PD + ONOFF-FOG: 5.2 (3.9, 6.4), PD-FOG: 5.0 (4.0, 5.9)
		[52]	**p = 0.001**	**↑ (0.83; 33 %) Training dataset: PD + FOG: 3.38 ± 2.35, PD-FOG: 2.55 ± 2.23**
			p = 0.002	**↑ (1.12; 34 %) Validation dataset: PD + FOG: 4.44 ± 3.65, PD-FOG: 3.32 ± 3.01**
		[38]	NS: p = 0.794	PD + FOG: 3.00 (2.00; 5.00), PD-FOG: 3.00 (2.00; 5.50)
RBDSQ4	2	[48]	NS: p = 0.445	PD + FOG: 2.33 ± 2.40, PD-FOG: 1.94 ± 2.32
		[47]	NS	Baseline: PD + FOG (transitional): 2.23 ± 2.35, PD-FOG: 1.64 ± 2.02
			p = 0.006	**↑ (1.05; 64 %) Baseline: PD + FOG (continuing): 2.69 ± 2.30, PD-FOG: 1.64 ± 2.02**
			NS	Follow up: PD + FOG (transitional): 2.73 ± 2.29, PD-FOG: 1.84 ± 2.02
			p = 0.006	**↑ (0.59; 36 %) Follow-up: PD + FOG (continuing): 2.63 ± 2.12, PD-FOG:1.84 ± 2.02**
RBDQ-HK: RBD, n (%)	3	[26]	NS: p = 0.641	PD + FOG: 28/64 (44 %), PD-FOG: 47/99 (48 %)
		[56]	**p = 0.001**	**↑ PD + FOG: 108/255 (42.35 %), PD-FOG: 209/712 (30.90 %)**
		[53]	**p = 0.030**	**↑ PD + FOG: 22/54 (40.7 %), PD-FOG: 106/399 (26.6 %)**
			NS: p = 0.630	After adjusted analysis
Polysomnography				
Tonic RSWA	2	[40]	**p < 0.007**	**↑ (20.6; 189 %) PD + FOG: 31.5 ± 15.7, PD-FOG: 10.9 ± 10.3**
		[46]	**p < 0.007**	**↑ (20.6; 189 %) PD + FOG: 31.5 ± 15.7, PD-FOG: 10.9 ± 10.3**
Phasic RSWA	2	[40]	NS: p = 0.059	PD + FOG: 7.1 ± 4.0, PD-FOG: 3.8 ± 4.0
		[46]	NS: p = 0.059	PD + FOG: 7.1 ± 4.0, PD-FOG: 3.8 ± 4.0
Total Sleep time, min	1	[40]	NS: p = 0.334	PD + FOG: 332.5 ± 54.9, PD-FOG: 337.1 ± 39.1
Sleep efficiency, %	1	[40]	NS: p = 0.341	PD + FOG: 79.8 ± 9.6, PD-FOG: 84.9 ± 6.4
Sleep latency, min	1	[40]	NS: p = 0.676	PD + FOG: 8.3 ± 7.9, PD-FOG: 4.7 ± 5.4
REM latency, min	1	[40]	NS: p = 0.203	PD + FOG: 82.8 ± 67.7, PD-FOG: 118.6 ± 65.6
N1 sleep, %	1	[40]	NS: p = 0.089	PD + FOG: 16.4 ± 7.9, PD-FOG: 13.4 ± 5.6
N2 sleep, %	1	[40]	NS: p = 0.444	PD + FOG: 55.3 ± 15.3, PD-FOG: 60.4 ± 12.9
N3 sleep, %	1	[40]	NS: p = 0.111	PD + FOG: 5.0 ± 8.2, PD-FOG: 6.7 ± 6.7
REM sleep, %	1	[40]	NS: p = 0.960	PD + FOG: 20.1 ± 12.4, PD-FOG: 19.6 ± 9.1
Daytime sleepiness				
ESS total	9	[40]	NS: p = 0.276	PD + FOG: 7.8 ± 3.7, PD-FOG: 8.9 ± 3.9
		[50]	**p = 0.009**	**↑ (1.0; 19 %) PD + FOG: 6.3 ± 3.3, PD-FOG: 5.3 ± 3.4**
		[39]	**p = 0.014**	**↑ (2.62; 53 %) Baseline: PD + FOG: 7.56 ± 3.74, PD-FOG: 4.94 ± 3.52**
			p = 0.003	**↑ (3.04; 45 %) Year 4: PD + FOG: 9.78 ± 4.71, PD-FOG: 6.74 ± 4.87**
		[26]	**p < 0.001**	**↑ (3; 60 %) PD + FOG: 8.0 (5.3–10.8), PD-FOG: 5.0 (3.0–7.0)**
		[56]	**p = 0.001**	**↑ PD + FOG: 104/255 (40.78 %), PD-FOG: 220/712 (30.90 %)**
		[15]	**p = 0.009**	**↑ (3.49; 47 %) PD + FOG: 10.89 ± 5.99, PD-FOG: 7.40 ± 5.95**
		[51]	NS: p = 0.259	PD + OFF-FOG: 7.8 (6.3, 9.3), PD + ONOFF-FOG: 9.1 (7.4, 10.9), PD-FOG: 7.6 (6.2, 9.0)
		[53]	**p = 0.001**	**↑ PD + FOG: 27/54 (50.0 %), PD-FOG: 109/399 (27.3 %)**
			p = 0.021	**After adjusted analysis**
		[38]	**p = 0.004**	**↑ (1; 20 %) PD + FOG: 6.00 (4.00;9.00), PD-FOG: 5.00 (3.00;6.50)**
JESS total	1	[55]	**p < 0.05**	**↑ (2; 50 %) PD + SFOG: 6.0 (3.0–9.75), PD-FOG: 4.0 (2.0–7.0)**
			p < 0.05	**↑ (2; 50 %) PD + CFOG: 6.0 (3.5–12.5), PD-FOG: 4.0 (2.0–7.0)**
Sleep quality				
PSQI total	6	[40]	NS: p = 0.235	PD + FOG: 7.5 ± 5.6, PD-FOG: 5.2 ± 2.7
		[49]	NS: p = 0.640	PD + FOG: 5.81 ± 3.05, PD-FOG: 6.13 ± 4.15
		[55]	**p < 0.01**	**↑ (2; 40 %) PD + SFOG: 7.0 (4.0–10.0), PD-FOG: 5.0 (3.0–7.75)**
			p < 0.01	**↑ (2; 40 %) PD + CFOG: 7.0 (5.0–10.0), PD-FOG: 5.0 (3.0–7.75)**
		[26]	**p < 0.01**	**↑ (4.5; 90 %) PD + FOG: 9.5 (6.0–12.8), PD-FOG: 5.0 (2.0–10.0)**
		[37]	**p < 0.05**	**↑ (4.4; 53 %) PD + FOG: 12.7 ± 2.6, PD-FOG: 8.3 ± 1.6**
			p = 0.001	**↑ (2.03; 30 %) Training dataset: PD + FOG: 10.08 ± 5.39, PD-FOG: 8.22 ± 5.30**
		[52]	**p < 0.0001**	**↑ (1.86; 23 %) Validation dataset: PD + FOG: 8.86 ± 4.8, PD-FOG: 6.83 ± 4.55**
Subjective sleep quality	2	[37]	**p < 0.05**	**↑ (0.9; 69 %) PD + FOG: 2.2 ± 0.6, PD-FOG: 1.3 ± 0.5**
		[26]	**p < 0.01**	**↑ PD + FOG: 2.0 (1.0–2.0), PD-FOG: 1.0 (0.0–2.0)**
Sleep latency	2	[37]	**p < 0.05**	**↑ (1; 77 %) PD + FOG: 2.3 ± 0.8, PD-FOG: 1.3 ± 0.6**
		[26]	**p = 0.001**	**↑ PD + FOG: 1.0 (0.0–2.0), PD-FOG: 0.0 (0.0–1.0)**
Sleep duration	2	[37]	**p < 0.05**	**↑ (0.9; 113 %) PD + FOG: 1.7 ± 0.5, PD-FOG: 0.8 ± 0.8**
		[26]	**p = 0.007**	**↑ (1.0; 100 %) PD + FOG: 2.0 (1.0–2.8), PD-FOG: 1.0 (0.0–2.0)**
Habitual sleep efficiency	2	[37]	**p < 0.05**	**↑ (0.5; 50 %) PD + FOG: 1.5 ± 0.9, PD-FOG: 1.0 ± 0.8**
		[26]	**p = 0.038**	**↑ PD + FOG: 1.0 (0.0–3.0), PD-FOG: 1.0 (0.0–2.0)**
Sleep disturbance	2	[37]	**p < 0.05**	**↑ (0.6; 40 %) PD + FOG: 2.1 ± 0.8, PD-FOG: 1.5 ± 0.7**
		[26]	**p = 0.001**	**↑ PD + FOG: 1.0 (1.0–1.0), PD-FOG: 1.0 (1.0–1.0)**
Sleep medication	2	[37]	NS: p > 0.05	PD + FOG: 1.5 ± 0.6, PD-FOG: 1.6 ± 0.8
		[26]	NS: p = 0.125	PD + FOG: 0.0 (0.0–0.0), PD-FOG: 0.0 (0.0–0.0)
Daytime dysfunction	2	[37]	**p < 0.05**	**↑ (0.8; 114 %) PD + FOG: 1.5 ± 0.9, PD-FOG: 0.7 ± 0.8**
		[26]	**p < 0.001**	**↑ (1.0; 100 %) PD + FOG: 2.0 (1.0–2.0), PD-FOG: 1.0 (0.0–2.0)**
Sleep disturbances				

Table 4 (*continued*)

Sleep parameters	Number of studies	Study	Significance	Results (mean ± SD or Median (IQR)) or direction of difference (↑↓) with absolute value
PDSS total	3	[26]	**p < 0.001**	↓ (10.5; 8 %) PD + FOG: 119.5 (109.3–128.8), PD-FOG: 130.0 (120.0–138.0)
		[56]	**p = 0.003**	↓ (5.74; 5 %) PD + FOG: 115.88 ± 26.08, PD-FOG: 121.62 ± 26.61
		[53]	**p = 0.005**	↓ (10; 8 %) PD + FOG: 116 (101–130), PD-FOG: 126 (109–141)
			p = 0.402	After adjusted analysis
NMSS	3	[20]	**p < 0.001**	↑ (5.25; 75 %) PD + FOG: 12.21 ± 10.09, PD-FOG: 6.96 ± 6.96
		[21]	**p < 0.007**	↑ (0.46; 25 %) PD + FOG: 2.34 ± 0.74, PD-FOG: 1.88 ± 0.52
		[54]	NS: p = 0.383	PD + FOG: 7.4 ± 7.9, PD-FOG: 6.8 ± 7.3 (severity)
			NS: p = 0.059	PD + FOG: 74 (87 %), PD-FOG: 106 (76 %) (frequency)
HAMD: Sleep disorder	1	[21]	**p < 0.001**	↑ (0.64; 40 %) PD + FOG: 2.25 ± 1.35, PD-FOG: 1.61 ± 1.24

PD + FOG: Parkinson's disease with freezing of gait; PD-FOG: Parkinson's disease without freezing of gait; CFOG: clinically observed FOG; SFOG: self-reported FOG; PD + EFOG: PD with H&Y stages 1 and 2; PD + AFOG: PD with H&Y stages 2.5–5; PD + FOG (transitional): PD reported 0 at baseline and ≥1 at follow up on the FOG-Q item 3; PD + FOG (continuing): PD reported ≥1 at baseline and follow up on the FOG-Q item 3; PD + ONOFF-FOG: levodopa-unresponsive FOG; PD + OFF-FOG: levodopa responsive FOG; REM: rapid eye movement; N1, N2, N3: sleep stages; RBDSQ: REM sleep behavior disorder screening questionnaire; RBDHK: REM sleep behavior disorder questionnaire Hong Kong; RSWA: REM sleep without atonia; ESS: Epworth sleepiness scale; JESS: Epworth sleepiness scale Japanese version; PSQI: Pittsburgh sleep quality index; PDSS: Parkinson's disease sleep scale; NMSS: non-motor symptoms scale; HAMD: Hamilton depression rating scale; IQR: interquartile range; SD: standard deviation.

Significance: significance between PD + FOG and PD-FOG; NS: not significant between PD + FOG and PD-FOG; **Significant results are marked in bold.**

↑: increase of values in PD + FOG compared with PD-FOG.

↓: decrease of values in PD + FOG compared with PD-FOG.

The PDSS [70] was utilized in three studies (15 %) ([53]; Tang et al. [56]), with a total of 1583 participants (30 %), comprising 1210 PD-FOG (76 %) and 373 PD + FOG (24 %). The PDSS serves as a reliable screening tool for evaluating sleep disturbances in PD over the previous week. It consists of 15 items, each scored on a visual analogue scale ranging from 0 to 10, where 0 represents severe and always experienced symptoms, and 10 indicates symptom-free status.

PDSS scores were significantly lower by 5.74 (5 %) [56] and a median of 10.5 [26] and 10.0 [53] in PD + FOG (n = 373) than PD-FOG (n = 1210). However, Lv et al. [53] found no significant difference in PDSS scores between both groups after adjusted analysis (p = 0.402).

The sleep disorders sub score in HAMD [71] was assessed in one study (5 %) [21] including a total of 248 participants (5 %), 120 PD-FOG (48 %) and 128 PD + FOG (52 %). It consists of three questions addressing insomnia early and middle of the night and early hours of the morning over the past week. The score ranges from 0 (no difficulty) to 2 (difficulty). The scores were increased by 0.64 (40 %) in PD + FOG compared with PD-FOG [21].

The sleep/fatigue domain of the NMSS [72] was reported in three studies (15 %) [20,21,54] including a total of 947 participants (18 %), 513 PD-FOG (54 %) and 434 PD + FOG (46 %). It consists of 4 items and was intended to assess the severity of symptoms with a score 0 (none) to 3 (severe) and frequency of symptoms with 1 (rarely) to 4 (very frequent) over the last month. The scores on sleep/fatigue domain showed contradicting results. The scores were higher by 5.25 (75 %) [20] and 0.46 (25 %) [21] in PD + FOG (n = 349) than PD-FOG (n = 373) in 2 studies [20,21]. Whereas, Ou et al. did not report significant difference between PD + FOG (n = 85) and PD-FOG (n = 140) groups on sleep/fatigue sub scores (NMSS severity: 7.4 ± 7.9 vs 6.8 ± 7.3, respectively; NMSS frequency: 74 (87 %) vs 106 (76 %), respectively) [54].

4. Discussion

To our knowledge, this systematic review is the first of its kind to identify and compare published studies focusing on sleep outcomes in PD + FOG and PD-FOG. The comprehensive analysis revealed that sleep disturbances, such as insomnia, RBD, sleep quality, and daytime sleepiness, were more pronounced in PD + FOG when compared to PD-FOG.

4.1. Sleep outcomes in PD + FOG and PD-FOG

RBD diagnosis typically requires a polysomnography recording, but screening and assessment can be conducted using questionnaires such as RBDSQ [63], RBDSQ4 [64], and RBDQ-HK [65], which were employed in the studies included in this review. The findings revealed that PD + FOG had higher scores in RBDSQ, RBDSQ4, and RBDQ-HK when compared to the PD-FOG group [13,39,47,50,52,55,56]. These higher scores suggest a higher likelihood of RBD and a greater severity/frequency of manifestations in PD + FOG. Additionally, the presence of RBD in PD was associated with cognitive impairment, such as dementia, and autonomic dysfunction [73]. RBD can disrupt sleep for both individuals and their partners, resulting in poor sleep quality and excessive daytime sleepiness [31].

Hall et al. conducted two studies [13,48] to explore phenotypic differences between PD patients with and without FOG and to investigate the prevalence of FOG and its association with disease progression. The first study [48] included PD patients in the early clinical stages of the disease (Hoehn and Yahr (H&Y) stage <3) and revealed no significant difference in RBDSQ and RBDSQ4 scores between PD + FOG and PD-FOG groups. Conversely, in the second study [13] comparing PD patients in the early disease stage (H&Y stage 1 and 2) to PD patients in the advanced disease stage (H&Y stage 2.5–5), the authors reported that PD + FOG had higher RBDSQ scores than PD-FOG in both groups, with a statistically significant difference observed only in the early stages of the disease. The authors attributed the discrepancy between these two studies to differences in the inclusion criteria, as the first study [48] employed stricter enrollment criteria with H&Y stage <3, indicating a potential role of disease progression [13].

Polysomnographic findings also suggest that abnormal muscle activity during REM sleep was more prominent in PD + FOG [40,46]. This observation aligns with the existing relationship between RSWA and PD + FOG [40]. Compared to PD-FOG, PD + FOG exhibited a notable 20.6 % increase in tonic EMG activity during REM sleep, indicating higher muscle activity instead of the usual low activity associated with muscle atonia [40,46]. Videnovic et al. demonstrated that this substantial difference in tonic RSWA between PD + FOG and PD-FOG persisted even after excluding PD patients with RBD (who exhibited dream enactment) from the analysis [40]. The amount of tonic EMG activity in PD + FOG was comparable to that found in PD patients diagnosed with RBD [40, 46]. Moreover, the lack of significant differences in other polysomnographic measures, such as total sleep time, sleep efficiency and latency, REM sleep latency, and the percentage of sleep during different sleep stages, between PD groups [40] suggests that the presence of FOG is not necessarily associated with more severe or distinct disruptions to overall sleep architecture in PD patients.

The presence of FOG has been associated with more frequent and severe sleep disturbances and worse disease outcomes. Conversely, the presence of RBD predicts an increased disease severity and a more rapid disease progression [52] and it has also been reported that tonic RSWA

in RBD could predict the development of PD [74]. Videnovic and colleagues confirmed that excessive tonic RSWA might predict the development of PD, mainly the subtype dominated by FOG and a tendency toward significance between PD + FOG and PD-FOG in terms of RSWA [40]. An association between RSWA and gait disturbances connected with FOG has also been reported [40,46]. The common neurodegenerative changes responsible for FOG in PD are implicated in the pathophysiology of RSWA in RBD, suggesting an underlying connection between these two phenomena [40]. Recent research has highlighted that FOG is caused by a disruption and atrophy in networks in the brainstem particularly the pedunculopontine nucleus [41]. These same networks are involved in the pathogenesis of RBD via their thalamic connections to the medial prefrontal and anterior cingulate cortices [41]. RBD was found to be associated with clinically assessed FOG but not with self-reported FOG, emphasizing the importance of objective clinical evaluation [55]. Additionally, PD patients with RBD have been shown to present a higher risk of developing FOG compared to those without RBD [75]. The proportion of PD patients with probable RBD is higher in the late stage of PD, and these individuals are more likely to develop FOG [76]. These findings suggest a bidirectional relationship between FOG and RBD in PD, possibly sharing common underlying mechanisms [40,41,46,52,55,75,76].

The association between FOG and RBD has been investigated not only based on the presence or absence of symptoms but also in terms of the severity of FOG. Higher RBDSQ4 scores were positively associated with FOG severity [47], indicating that sleep disturbances may worsen as FOG onset approaches or that both FOG and sleep disturbances occur simultaneously due to shared neuroanatomical structures and networks, such as the pedunculopontine nucleus [47].

This could also explain the increased bidirectional association in incidence between FOG and RBD. The PPN has been implicated in sleep-wake cycles and the integration of gait control and sleep function [77, 78]. However, not all studies have consistently demonstrated an association between sleep disturbances and FOG. Some studies found no differences in RBD prevalence between PD + FOG and PD-FOG groups [15,48], and no association between the Non-Motor Symptoms Questionnaire (NFOG-Q) and RBDSQ scores [15]. These findings suggest that the interplay between sleep disturbances and FOG may be more complex, and the association between the two pathological processes in the brainstem, especially in early disease stages, may not be strong [48].

The current review highlights that PD + FOG patients experience more frequent and severe daytime sleepiness compared to PD-FOG individuals. Daytime sleepiness was evaluated using various questionnaires, such as the Epworth Sleepiness Scale (ESS) [67] and the Japanese version of the Epworth Sleepiness Scale (JESS) [68]. Multiple studies demonstrated higher scores in PD + FOG groups, indicating more pronounced daytime sleepiness and sleep/fatigue symptom severity [15,26, 39,50,55,56]. Excessive daytime sleepiness might result from impaired nighttime sleep and subsequent sleep deprivation or be a complication of the disease, involving neurodegeneration of sleep and wake areas as well as the influence of PD medications [26]. The pathophysiology of excessive daytime sleepiness has been linked to structural and neurochemical damages, including degeneration in regions like the locus coeruleus, hypothalamus, and ascending reticular activating system (ARAS), which are vital in regulating sleep and wakefulness coordination [79]. Moreover, deficits in noradrenaline, serotonin, and dopamine have also been implicated in the development of excessive daytime sleepiness [79]. Unlike RBD, daytime sleepiness showed an association with both clinically assessed and self-reported FOG [55].

However, a study by Zhang et al. [15] failed to find a correlation between the Non-Motor Symptoms Questionnaire (NFOG-Q) and the Epworth Sleepiness Scale (ESS) [15]. Excessive fatigue might be an explanation for this finding, as fatigue can be related to daytime sleepiness in PD but can also occur independently in patients who do not experience sleepiness [80]. It is worth noting that patients may not always accurately differentiate between fatigue and excessive sleepiness

when subjectively reporting their symptoms [80]. Conversely, Xu et al. [56] reported that PD + FOG had higher scores on the Parkinson's Disease Fatigue Scale, indicating more fatigue compared to PD-FOG [56]. This suggests that the higher daytime sleepiness observed in PD + FOG might be a result of excessive fatigue. However, distinguishing between fatigue and excessive daytime sleepiness could be challenging for some patients, as some individuals who report feeling fatigued might actually be experiencing excessive sleepiness [81].

In the studies reporting more excessive daytime sleepiness in PD + FOG [15,26,53,56], the levodopa equivalent daily dosage was also higher in PD + FOG, suggesting a possible relationship between daytime sleepiness and levodopa in these patients. Previous research by Arnulf and Leu-Semenescu [82] indicated that levodopa and dopamine agonists might contribute to or exacerbate daytime sleepiness due to their sedative effects.

Overall, the relationship between excessive daytime sleepiness, fatigue, and medication in PD + FOG patients remains complex and warrants further investigation to better understand the underlying mechanisms and potential interventions to manage these symptoms effectively.

The findings of the present review suggest that PD + FOG patients experience worse overall sleep quality compared to PD-FOG. The Pittsburgh Sleep Quality Index (PSQI) was commonly used to assess general sleep quality, and higher PSQI scores were observed in PD + FOG compared to PD-FOG, indicating poorer sleep quality [26,37,52,55,69], regardless of whether FOG was clinically assessed or self-reported [55]. In addition to lower sleep quality, PD + FOG patients showed reduced sleep duration, efficiency, and increased sleep onset latency, along with a higher frequency of sleep disturbances and lower daytime functioning compared to PD-FOG patients [26,37]. These sleep disturbances were also observed when comparing PD + FOG to age-matched healthy controls [37].

Furthermore, PSQI scores in PD + FOG patients were positively correlated with scores on the Non-Motor Symptoms Questionnaire (NFOG-Q) and with cognitive, mobility, and anxiety scores, which are known predictors of FOG and its underlying components [37]. Authors explained these findings by the relationship between sleep and decreased functional connectivity of gait and arousal networks in PD + FOG, specifically involving the pedunculopontine nucleus (PPN), supplementary motor area, and cingulate cortex [37].

However, one longitudinal study [49] did not find an association between sleep quality assessed by PSQI and the development of FOG over a 5-year observation period. The authors suggested that the timing of the assessment relative to the occurrence of FOG might have played a role, and assessing sleep quality closer to the development of FOG could have revealed a significant association [49].

When specifically considering scales designed to assess sleep in PD patients, such as the Parkinson's Disease Sleep Scale (PDSS), PD + FOG patients tended to have lower PDSS scores compared to PD-FOG, indicating a higher frequency of sleep disturbances in PD + FOG [26,53,56, 70]. In a prospective study, authors found a higher incidence of FOG in PD patients with low scores on the PDSS first item, which assesses the overall quality of night's sleep (PDSS1) [26], further highlighting the bidirectional association between sleep disturbances and FOG.

Additionally, in the aforementioned studies [26,53,56], PD + FOG patients had worse PDSS scores and were prescribed a higher levodopa equivalent daily dose compared to PD-FOG patients, suggesting a relationship between sleep and medication, with the latter potentially impacting sleep disturbances. Interestingly, a recent study [83] reported that the use of a triple combination of levodopa/carbidopa/entacapone at night improved sleep symptoms evaluated using the PDSS, specifically sleep onset, sleep maintenance, and RBD, particularly in PD patients with worse baseline PDSS scores, which corresponds to the PD + FOG group in this study. This suggests that levodopa/carbidopa/entacapone combination could be a potential treatment for PD patients with sleep disturbances.

Insomnia, on the other hand, was evaluated using the sleep disorders sub-score in the Hamilton Depression Rating Scale (HAMD), with higher scores indicating more severe insomnia. PD + FOG patients had higher scores on the sleep disorder sub-score, indicating a higher prevalence of insomnia in this group [21]. Furthermore, higher sleep disorder scores were associated with FOG [21]. The authors also reported that PD + FOG patients had higher scores on perceptual problems/hallucinations on the Non-Motor Symptoms Scale (NMSS) and displayed an akinetic rigid style [21]. Other studies [84,85] suggested various factors contributing to insomnia in PD, including hallucinations, rigidity, and akinesia. Additionally, FOG was associated with the early use of levodopa and a higher daily dose of levodopa. A recent review [86] reported an association between dopaminergic medications and insomnia, with medications potentially increasing the risk of insomnia. However, it is worth noting that the HAMD scale is not specifically designed for evaluating insomnia in PD.

5. Limitations and future direction

Although this review provides valuable insights into sleep outcomes in PD + FOG compared to PD-FOG, there are certain limitations that should be acknowledged. Firstly, the number of included studies (n = 20) was relatively small, with a total of 3049 PD-FOG (58 %) and 2163 PD + FOG (42 %) participants. Furthermore, the sample sizes of the included studies were highly heterogeneous, and some studies had small cohorts (Table 3).

Secondly, the assessment methods used for sleep and FOG were not consistent across studies. While the reported scales are validated tools, most of the sleep assessments relied on subjective scales, and only two studies conducted polysomnography as an objective method to evaluate sleep disturbances [40,46]. Additionally, many studies used scales that were not specifically developed to assess sleep in PD patients, with only two studies utilizing the PDSS scale [26,56]. It is worth mentioning that subjective and objective assessment methods for sleep could yield contradictory results [87], and a combination of both approaches might be beneficial in estimating sleep disorders [88].

Similarly, most assessments of FOG were subjective, relying on patient recall and potentially introducing biases [15]. Clinical observation of FOG was sometimes performed by the patients themselves, which could be influenced by educational level and correct understanding of FOG, leading to errors and biases [56]. However, some studies suggested that self-reported questionnaires, like the NFOGQ, could be more useful for screening FOG [55]. A combination of both subjective and objective methods for FOG assessment, such as wearable or real-time monitoring systems, could provide valuable insights and are needed in further research.

Additionally, the follow-up periods of 1–3 years in some studies may be too short to detect the onset of FOG, which could explain the low incidence of FOG in certain longitudinal studies [56]. Furthermore, medication status during FOG assessment was not consistently reported in the studies. Considering that FOG episodes occur more frequently in the "OFF" state, but can also occur in the "ON" state, conducting evaluations in both states may be helpful for a comprehensive understanding of FOG occurrence.

Additionally, it is worth noting that some PD patients in the included studies were using medications like clonazepam to address their sleep problems, which might potentially influence RBD symptoms, gait performance, and even impact the occurrence of FOG [46]. In light of this, both pharmacologic and non-pharmacologic treatment options, such as physical activity and exercise, have been explored to enhance sleep quality in PD [89]. Physical activity has been recognized as a beneficial approach in managing PD [90], and several studies have investigated its effect on sleep quality in PD patients, with indications that exercise could lead to an improvement in sleep disorders and overall sleep quality [91].

As we look ahead, an exciting avenue for future research lies in systematically measuring the effects of sleep enhancement interventions on the frequency and intensity of FOG episodes. A crucial aspect of this research would involve developing more accurate methods to diagnose RBD in the absence of polysomnography. To achieve this, researchers may explore the comparative effectiveness of various RBD questionnaires in relation to FOG symptoms. However, to ensure robust and reliable findings, the inclusion of PD patients with PSG-confirmed REM sleep behavior disorder would be imperative. By focusing on this subset of patients, researchers can gain deeper insights into the interplay between RBD, sleep quality, and the occurrence of FOG. This targeted analysis promises to be an intriguing and valuable facet of future investigations.

6. Conclusion

In summary, this systematic review provides an overview of the literature on sleep outcomes in PD + FOG compared to PD-FOG. Despite a relatively limited number of studies and some inconsistencies, the evidence suggests that PD + FOG patients experience worse sleep quality, increased daytime sleepiness, and more frequent and severe sleep disturbances than PD-FOG patients. To gain a deeper understanding of the relationship between FOG and sleep disturbances, future longitudinal studies should employ both objective and subjective sleep and FOG assessments over an extended observation period. Finally, investigating the potential impact of improving sleep quality on FOG occurrence and vice-versa could be a crucial topic for future research endeavours.

Institutional Review Board statement

Review articles do not require Institutional Review Board (IRB) approval if the data reviewed are public (including private and government databases) and if the articles reviewed have received IRB approval previously.

Informed consent statement

Not applicable.

Data availability statement

Not applicable.

CRediT authorship contribution statement

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Declaration of competing interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2023.11.021.

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