

Association between Sleep Disorders and Risk of Parkinson's Disease: A Systematic Review and Meta-Analytical Study

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ABSTRACT

Background: Sleep–wake disturbance is an early non-motor symptom of Parkinson's disease (PD), but whether sleep disorders are prodromal manifestations or upstream aetiological factors remains unclear. Given that the PD prodrome may exceed 20 years, we combined longitudinal evidence to assess associations between sleep disorders and incident PD, rank disorders by association strength, and identify potential prodromal markers among candidate causal exposures.

Methods: Review six databases of studies that determined sleep exposure prior to incident PD (1990-present until June 2026 plus landmark studies) compliant with PRISMA 2020. The Newcastle–Ottawa scale, ROBINS-E, QUIPS and QUADAS-2 were used to assess the presence of bias. Random-effects models with Hartung–Knapp–Sidik–Jonkman correction were pre-specified, with heterogeneity quantified as Cochran's Q and I^2 , τ^2 and prediction intervals.

Results: Thirty-four reports were added, including 18 longitudinal studies, 11 meta-analyses, and 5 genetic studies. iRBD showed the strongest association with PD, with phenoconversion of 6.25%/year and 73.5% at 12 years. Insomnia remained predictive beyond 20 years (IRR 1.37, 95% CI 1.13–1.66). Excessive daytime sleepiness, prolonged napping, and reduced circadian amplitude showed moderate associations, whereas evidence for OSA was contradictory and no association was observed for restless legs syndrome.

Conclusion: Only one sleep disorder (iRBD) has high-certainty evidence of being a prodromal synucleinopathy; only one of them (insomnia) has credible evidence of aetiological contribution. OSAS, restless legs syndrome and sleep duration have not been established.

Key-words: Parkinson's disease; REM sleep behaviour disorder; Insomnia; Prodromal markers; Obstructive sleep apnoea; Circadian rhythm; Meta-analysis; α -synuclein

INTRODUCTION

Parkinson's is the world's fastest growing neurological disability burden condition. In 2021, there were an estimated 11.77 million people living with PD (1.335 million incident cases, 7.472 million disability-adjusted life-years lost) and the prevalence in 2050 is projected to be 25.2 million ^[1–4].

There is no disease-modifying treatment, and thus the two mechanisms that could be leveraged are the identification of modifiable risk factors and detection of disease before irreversible nigral loss.

Pathologically PD is characterized by nigral degeneration of dopaminergic system accompanied by accumulation of misfolded α -synuclein. Braak and colleagues suggested that the process was caudorostral, with Lewy pathology first appearing in the dorsal motor vagal nucleus, old and new olfactory structures, and pontomedullary tegmentum (stages 1-2) before moving on to the substantia nigra (stages 3-4) ^[5]. This is predictive of a long clinically silent period and, importantly, that the brainstem nuclei that form REM

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muscle atonia are targeted prior to nigra. The Movement Disorder Society (MDS) formalized this in research criteria that included a prior probability based on age along with the likelihood ratios of the markers [6,7].

Anatomical and mechanistic is the rationale for studying sleep. All major sleep–wake generators (locus coeruleus, raphe, pedunculopontine nucleus, hypothalamic orexin neurons and suprachiasmatic nucleus) are destroyed in PD, meaning sleep disturbances are likely to be present early in the disease. On the other hand, glymphatic clearance of extracellular α -synuclein is sleep-dependent and highest in slow wave sleep, therefore chronic sleep disruption may be a possible cause for aggregation. Long-latency designs, lag analyses and genetic triangulation are the only ways to distinguish between both directions of generation, which produce identical signals over short follow-up. Current reviews focus on specific disorders and do not generally stratify or segregate by ascertainment or follow-up length. Therefore, we set out to quantify the association of each disorder with incident PD, rank them by strength and certainty and classify disorders as prodromal markers, candidate causal factors, or unestablished.

MATERIALS AND METHODS

Design, question and PECOS framework- Systematic review with meta-analysis reported as per PRISMA 2020 [37] and MOOSE. The PECOS frame was: adults without prevalent PD or parkinsonism; the sleep disorders and measures listed in Table 2; comparators without the index disorder or the reference stratum; incident PD, with parkinsonism, dementia with Lewy bodies and composite phenoconversion secondary; and prospective, registry, multicentre clinical, case–control and diagnostic-accuracy designs.

Search, Eligibility and Selection- All search strings for each sleep disorder and measure, and longitudinal risk (full strings in the Supplement), were combined with PD and synucleinopathy, and were searched with PubMed/MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, medRxiv, from 1st January 2010 up to 30th June 2026, without date restriction; major neurology and sleep journals were handsearched and citations chased bidirectionally. Studies had to meet the following criteria to be included: exposure must have come before outcome; exposure must have been

defined by a validated instrument, actigraphy or a specified administrative case definition, or by video-polysomnography and/or ICSD-2/3 criteria; ascertainment of PD must have relied on a clinical diagnosis or a validated register linkage; and the effect estimate and 95% confidence interval must have been provided or calculated. The cross-sectional or prevalence-only designs and exposure ascertained after diagnosis or exposure in the form of secondary sleep disorders and series with less than ten patients were excluded. Multiple reports from different cohorts (MrOS, Taiwanese and Korean insurance databases, UK Biobank and International RBD Study Group) were used for different exposures, but were not combined into one. The process of screening and extraction was repeated with adjudication.

Risk of bias and Statistical analysis- Cohort and case–control studies were rated for Newcastle–Ottawa Scale [43]; iRBD phenoconversion-predictor analyses and RBD screeners were rated for QUADAS-2 [50] and for the Newcastle–Ottawa Scale [43]; GRADE [43] was used to rate certainty. Where fewer than ten original studies contributed, log hazard ratios were pooled with the inverse-variance random-effects model with the Hartung–Knapp–Sidik–Jonkman correction; hazard, rate and relative risks were treated as interchangeable with a rare outcome; case–control and prevalence odds were pooled separately; and fixed-effects models were applied solely for sensitivity.

Cochran's Q , I^2 [39], τ^2 and prediction intervals were used to quantify heterogeneity, as was a priori restricted publication bias by funnel plots accompanied by Egger's [40] test and Begg's [41] test, and as was a priori restricted meta-regression of heterogeneity. Pre-specified subgroups were ascertained, design, setting, duration of follow-up, lag application, region, sex and age, and E models of models for competing risk [44,45] analysis. The conditions described above were not satisfied for iRBD, RLS, EDS, circadian disruption and sleep architecture, and these strata were thus synthesized narratively, which is reported as a finding and not hidden. The data analyses were carried out with R 4.2.2 and Stata 17.

RESULTS

Thirty-four reports were eligible: 18 primary longitudinal studies with over 800,000 participants and over 5,600 incident PD cases (when event counts were reported); 11 meta-analyses; and 5 genetic studies (Table 1). The best

phenotyped cohorts (MrOS, the International RBD Study Group) had the least events (43–352; 8,19,22,25) while single self-report items and/or diagnostic codes were used in the largest cohorts [12,26,27].

Fig. 1: PRISMA 2020 flow diagram of study identification, screening, and inclusion

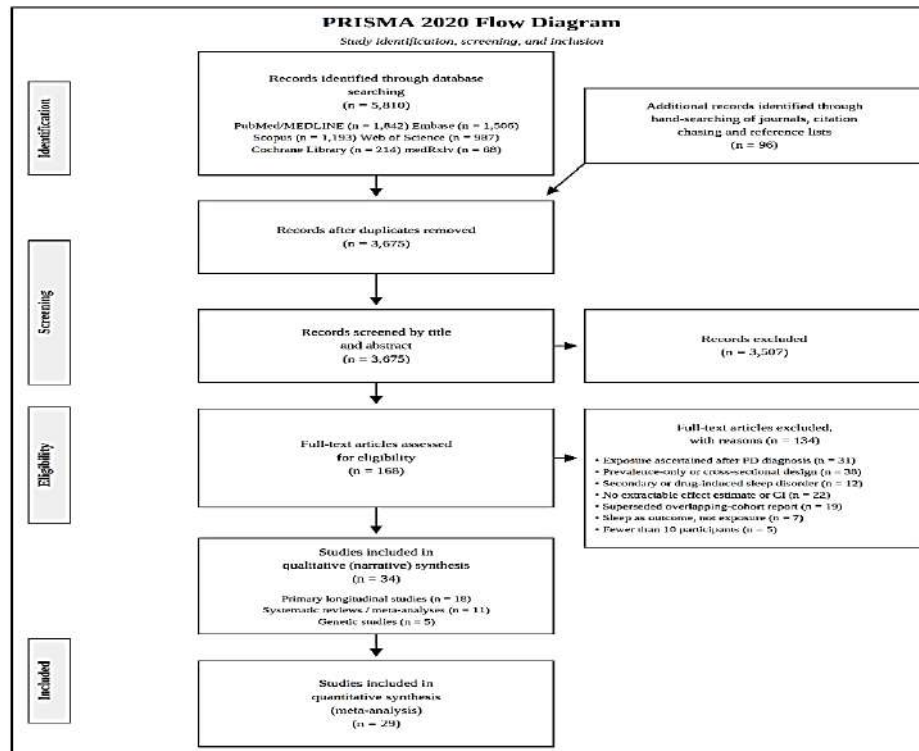


Table 1: Characteristics of included studies

Study	Design	Population	N (PD events)	Age; % male	Region	Follow-up	Exposure ascertainment
Postuma [8]	Multicentre clinical cohort	Isolated RBD	1,280 (352)	66.3±8.4; 82.5	24 centres, 4 continents	Mean 3.6 y; 4,890 py	Video-PSG
Galbiati [9]	Meta-analysis, longitudinal	Isolated RBD	Not stated	—	Multinational	Mean 4.75±2.43 y	Video-PSG
Iranzo [10]	Prospective cohort	Isolated RBD	174 (65)	Median 69	Spain	Median 4 y	Video-PSG
Sulkava [11]	Prospective population cohort	General population	71,718 (2,679)	45.7±12.3; mixed	Finland	Mean 24.6±12.4 y	Single self-report item; polygenic score
Hsiao [12]	Registry cohort	Non-apnoea sleep disorders	182,546	Mixed	Taiwan	To 2010	ICD codes
Lysen [13]	Prospective population cohort	General population	7,726 (75)	65; 43	Netherlands	Mean 8.4 y	PSQI



Sun ^[14]	Meta-analysis	OSA	12 studies; 93,332	Mixed	Multinational	Varied	Mixed
medRxiv ^[15]	Meta-analysis	OSA	6 studies; >1.1 million	Mixed	Multinational	Varied	ICD codes/PSG
Zeng ^[16]	Meta-analysis, cross-sectional	PD vs controls	322/6,361	—	Multinational	—	PSG
Maggi ^[17]	Meta-analysis, prevalence	Established PD	16 studies; 1,448	Mixed	Multinational	—	PSG
Abbott ^[18]	Prospective cohort	Elderly men	3,078 (43)	71–93; 100	Hawaii	1991–2001	ESS/interview
Leng ^[19]	Prospective cohort	Elderly men (MrOS)	2,920 (106)	76; 100	USA	11 y	ESS + actigraphy
Bang ^[20]	Registry cohort	Incident RLS	19,838 (257)	≈50; 37.2	Korea	2002–2019	ICD-10 G25.8 (≥2 visits)
Leng ^[22]	Prospective cohort	Elderly men (MrOS)	2,930 (78)	76.3±5.5; 100	USA	11 y	Wrist actigraphy, cosinor
Chen ^[23]	Prospective cohort	Female nurses	84,794 (181)	—; 0	USA	975,912 py	Self-reported shift work
Sohail ^[24]	Clinicopathological cohort	Older adults without PD	Autopsy series	Mixed	USA	To death	Actigraphy
MrOS ^[25]	Prospective cohort	Elderly men (MrOS)	2,770 (70)	≥67; 100	USA	Median ~10 y	Overnight PSG + qEEG
Chen ^[26]	Prospective cohort	UK Biobank	339,666 (1,966)	Mixed	UK	Median 11.8 y	5-item sleep pattern

py, person-years; PSG, polysomnography; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; qEEG, quantitative electroencephalography.

Overall association- These were modest estimates: HR 1.18 (1.11–1.26) in 91,273 Taiwanese patients with non-apnoea sleep disorders and matched controls (12); and HR 0.78 (0.69–0.87) in 339,666 UK Biobank participants

(26) with relaxation of causality after adjustment because of the possibility that patients had lower-quality sleep. The explorer message lies in the analyses of the disorder (Table 2).

Table 2: Major sleep disorders and their association with Parkinson's disease

Sleep disorder	Principal mechanism	Direction and strength	Recognised in MDS criteria
Isolated RBD (PSG-confirmed)	Braak stage 1–2 degeneration of sublaterodorsal/ventromedial medullary REM-atonia circuitry	Very strong, dose-dependent with time	Yes (LR+ 130)
Probable RBD (questionnaire)	Same, but low specificity	Weak	Yes (LR+ 2.8)
Insomnia	Hyperarousal, HPA overactivity, reduced slow-wave sleep, impaired glymphatic clearance	Modest, persistent, dose-dependent	No

Obstructive sleep apnoea	Intermittent hypoxia, oxidative stress, neuroinflammation	Contradictory across designs	No
Excessive daytime sleepiness / napping	Degeneration of orexinergic, noradrenergic, cholinergic wake systems	Moderate; objective > subjective	Yes (EDS, LR+ 2.7)
Restless legs syndrome	Brain iron deficiency, A11 diencephalospinal pathway; non-degenerative	Negligible absolute effect	No
Circadian rhythm disruption	Suprachiasmatic dysfunction, melatonin suppression, clock-gene dysregulation	Moderate; amplitude not timing	No
Sleep fragmentation / EEG slowing	Reduced slow-wave sleep; thalamocortical dysfunction	Moderate; directions inconsistent	No
Sleep duration (short or long)	Reverse causation (prodromal hypersomnolence)	Null after long follow-up	No
Periodic limb movements	Unknown	Not studied prospectively	No

REM sleep behaviour disorder- iRBD was both quantitatively and mechanistically unique. In 1,280 patients (from 24 centres) with polysomnography confirmation of a diagnosis, 352 (28%) phenoconverted at a rate of 6.25 per year (cumulative risk of 31.3% after 5 years, 60.2% after 10 years and 73.5% after 12 years), with parkinsonism as the first manifestation in 56.5% and dementia in 43.5% [8]. A meta-analysis of longitudinal studies followed by this group showed 33.5%, 82.4% and 96.6% at 5, 10.5 and 14 years respectively; 43% of the converters had been diagnosed as PD [9]; and the independent cohort reported 33.1%, 75.7% and 90.9% at 5, 10 and 14 years respectively, with all 6 cases followed with post mortality diagnosis of Lewy pathology [10]. The concordance between the 3 sources of the 5-year estimates (31.3%, 33.5%, 33.1%) is unique in this literature, and the absence of any marked effect except for beyond age 60 [36], when the general-population iRBD prevalence is ~1%, suggests marked enrichment [35].

There are two features which dictate the way that RBD has to be handled analytically. The LR+ of the MDS criteria for RBD (130) is significantly higher than an abnormal dopaminergic scan (43.3), and the questionnaire-defined possible RBD only 2.8 (7), which is a difference of 46 fold — stratifying was therefore warranted to make pooling of the two groups defensible. Second, none of the other sleep disorders had predictive value within iRBD: insomnia (HR 0.90–1.16), daytime somnolence (HR 0.94–1.71), RLS and apnoea–hypopnoea index ≥ 15 (all HR 0.90–1.16); all motor, olfactory,

cognitive and autonomic markers had strong predictive value (1.54–3.16); combined MDS criteria best of all (5.37, 2.77–10.4). They are nulls in a condition where it is already known that the process is in a prodromal state, rather than are nulls that rule out population level associations.

Insomnia- The only evidence that could support causality was insomnia. Among 71,718 Finnish participants followed a mean 24.6 years (2,679 events), insomnia reported "sometimes" and "often" gave incidence rate ratios (IRR) of 1.14 (1.05–1.24) and 1.54 (1.35–1.75) in a dose–response pattern [11]. The association was retained for frequent insomnia (1.37, 1.13–1.66), abolished for occasional insomnia (1.06, 0.94–1.18) (expected if the more powerful exposure is aetiological and the less powerful is prodromal) and an insomnia polygenic score was independently associated with PD (1.13, 1.05–1.23), with sleep-duration scores null. The E-value for cardiovascular risks was 2.45, and the highest contributor of the E-value was prodromal contamination, which was unlikely in the youngest stratum of the baseline study (<35 years, 1.66, 1.01–2.71); the largest non-apnoea subgroup was chronic insomnia (1.37, 1.21–1.55) in Taiwan [12]. In the Rotterdam Study, subjective sleep quality also showed no association with parkinsonism over a period of 13 years after adjustment for the reverse causal relationship (increase in the first two years) [13], and Mendelian randomisation consistently showed no causal association [28,29].

Obstructive sleep apnoea- The evidence for OSA was the most confusing in this review. HRs in registry based syntheses were positive: 12 studies reporting 93,332 cases led to a pooled HR of 1.59 (1.36–1.85) which was essentially the same in men and women ^[14] and 6 studies reporting 1.1 million individuals led to a HR of 1.64 (1.56–1.73) ^[15]. However, the prevalence of OSA was lower in PD patients (OR 0.60, 0.44–0.81) and complete homogeneity was observed ($I^2=0\%$; $\chi^2=3.90$, $P=0.420$), largely due to the reduced BMI of the patients with PD ^[16]. Minimal oxygen saturation in REM sleep was associated with increased risk of incident PD (but not apnoea-hypopnoea index) and there was no association with apnoea-hypopnoea index in iRBD. The pooled prevalence of OSA in established PD was 44% (35–54; $I^2=91.0\%$), which was associated with age, BMI, motor severity and treatment with dopamine agonists, and inversely with RBD ^[17]. This would most likely reflect surveillance bias and cardiometabolic confounding in the claims cohort, with an added secondary increase in OSA upon diagnosis.

Excessive daytime sleepiness, napping and hypersomnia- In the Honolulu–Asia Aging Study, 43 incident cases were obtained from 3,078 men aged 71–93 years; EDS was associated with an age adjusted OR of 3.3 (1.4–7.0) and to 2.8 (1.1–6.4) after full adjustment, while insomnia was not related ^[18]. Objective measurement (actigraphic napping ≥ 1 h/day without EDS) had an OR of 1.96 (1.25–3.08) and 2.52 (1.21–5.27) for a 2-year lag ^[19]; no results were significant for EDS alone. EDS has an LR+ of 2.7 (7), and with RBD, one of only two recognised sleep markers.

Restless legs syndrome- There were 9,919 patients with RLS and 9,919 matched controls; due to the violation of proportional hazards, the difference in incidence of PD over 15 years was reported as restricted mean survival time (RMST) (-0.07, -0.11; $p=0.00$) or -0.05 years or about 18 days (-0.03, -0.07; $p=0.001$). The difference was larger in untreated patients and longer in dopamine-agonist-treated patients, but cannot be separated in the latter from neuroprotection from diagnose-masking. The accompanying editorial called the interpretation into question ^[21] and RLS was absent in iRBD ^[8]; the absolute effect is very small and the possibility of overlap with prodromal PD leg symptoms has not been ruled out.

Circadian rhythm disruption- This was reinforced by increasing the OR with decreasing amplitude of rest–activity (1.77, 1.30–2.41; $P<0.005$); mesor (1.64); and robustness (1.54) with lowest vs highest quartile ORs of 3.11, 3.04 and 2.65, but not by timing of the rhythm ^[22] even after adjusting for sleep disturbance at night and excluding cases within 2 years of recruitment — suggesting that signal is associated with rhythm strength rather than timing. However, in 84,794 nurses, a period of 15+ years of rotating night-shift work was related to decreased risk (relative risk 0.50, 0.26–0.97) ^[23], which is most likely to be explained by a pre-established pattern of shift-work avoidance in predromal diseases.

Sleep fragmentation, sleep architecture and sleep duration- This is because greater actigraphic sleep fragmentation in older adults who did not have clinical PD was independently associated at autopsy with Lewy body pathology (OR 1.40, 1.05–1.86), nigral neuronal loss (1.43, 1.10–1.88) and a pathological diagnosis of PD (2.04, 1.34–3.16), in the absence of any parkinsonian signs or comorbidity ^[24] - the strongest evidence for disturbed sleep being related to the pathology, not only to the diagnosis. Mixed results were found with polysomnography: higher total sleep time and lower REM percentage and lower non-REM α/θ ratio predicted PD; the lowest quartile of α/θ ratio was associated with an OR of 3.71 (1.8–7.7) while a higher awakening index was protective (25 events). To determine the association of sleep duration with a polygenic score, the association was kept restricted to a maximum of 20 years; for >9 h, the association of sleep duration with the polygenetic score was null, and all sleep-duration polygenetic scores were null ^[11]; periodic limb movement disorder has not been studied yet in a prospective manner.

Comparative analysis, heterogeneity and publication bias- There was no suitable stratum available with sufficient paired sensitivity–specificity data for bivariate modelling; as a result, comparative predictive strength is presented as a risk plot. The order is clear (Table 4): confirmed iRBD is more than an order of magnitude stronger than all other exposures; insomnia, EDS/napping, "circadian amplitude loss" and "electroencephalographic slowing" make up an intermediate tier (1.4–3.7); OSA, RLS and sleep duration fall in a weak, contradictory or null group of exposures.



The disorders in Table 5 can be placed on the "prodromal" timeline. Heterogeneity was not due to disorder: registry cohorts of OSA ($I^2=23.8\%$) and prevalence-odds studies ($I^2=0\%$) were homogeneous, but not the prevalence in established PD ($I^2=91.0\%$)^[17], and the RBD-symptom estimate dropped from OR 5.69 to

3.54 ($I^2=70.5\%$ to 0%) after three "outliers" were removed (49). Publication bias could only be evaluated for OSA; the other three to five studies did not provide informative results from Begg's ($p=0.806$) or Egger's test ($p=0.728$).

Table 3: Comparative quantitative risk estimates

Exposure	Estimate (95% CI)	Source
Isolated RBD, annual phenoconversion	6.25%/y; 31.3% at 5 y; 73.5% at 12 y	[8]
Isolated RBD, cumulative risk	33.5% at 5 y; 82.4% at 10.5 y; 96.6% at 14 y	[9]
PSG-proven RBD, likelihood ratio	LR+ 130	[7]
Insomnia "often" (cause-specific)	IRR 1.54 (1.35–1.75)	[11]
Insomnia "often" (>20 y follow-up)	IRR 1.37 (1.13–1.66)	[11]
Insomnia "often" (Fine–Gray)	HR 1.26 (1.11–1.43)	[11]
Insomnia polygenic score	IRR 1.13 (1.05–1.23)	[11]
Chronic insomnia >3 months	aHR 1.37 (1.21–1.55)	[12]
Any non-apnoea sleep disorder	aHR 1.18 (1.11–1.26)	[12]
OSA, pooled (12 studies)	HR 1.59 (1.36–1.85)	[14]
OSA, pooled (6 studies)	HR 1.64 (1.56–1.73), $I^2=23.8\%$	[15]
OSA prevalence in PD vs controls	OR 0.60 (0.44–0.81), $I^2=0\%$	[16]
EDS, fully adjusted	OR 2.8 (1.1–6.4)	[18]
Objective napping ≥ 1 h/day	OR 1.96 (1.25–3.08)	[19]
EDS + napping ≥ 1 h/day	OR 2.52 (1.21–5.27)	[19]
RLS (restricted mean survival time, $\tau=15$ y)	–0.05 y (–0.07 to –0.03)	[20]
Circadian amplitude, per 1-SD decrease	OR 1.77 (1.30–2.41)	[22]
Circadian amplitude, lowest vs highest quartile	OR 3.11 (1.54–6.29)	[22]
Night-shift work ≥ 15 y	RR 0.50 (0.26–0.97)	[23]
Sleep fragmentation → pathological PD diagnosis	OR 2.04 (1.34–3.16)	[24]
Non-REM α/θ , lowest vs highest quartile	OR 3.71 (1.8–7.7)	[25]
Sleep <7 h / >8 h	IRR 1.00 (0.84–1.18) / 1.01 (0.86–1.20)	[11]
Ideal sleep pattern (composite)	HR 0.78 (0.69–0.87)	[26]

Table 4: Quality assessment and strength of evidence

Exposure	Independent cohorts	Objective ascertainment	Survives long follow-up or lag	Genetic support	GRADE certainty
Isolated RBD (PSG)	≥ 24 centres + 2 meta-analyses	Yes	Yes (to 14 y)	Yes	High
Insomnia (frequent)	≥ 3	Partial	Yes (>20 y)	Yes	Moderate
EDS / objective napping	2	Yes	Partial (11 y, 2-y lag)	No	Moderate

Circadian amplitude loss	1 strong + 1 large	Yes	Partial (2-y exclusion)	No	Low–moderate
Sleep architecture / EEG slowing	1	Yes	Partial	No	Low
Obstructive sleep apnoea	12 studies, region-restricted	Yes, but null	No	No	Low (contradictory)
Restless legs syndrome	1 registry (null in iRBD)	No	Not tested	No	Very low–low
Sleep duration	≥4	Partial	No (vanishes >20 y)	No (all null)	Very low
Periodic limb movements	0	—	—	—	Insufficient

Table 5: Clinical interpretation of major sleep disorders as prodromal markers

Disorder	Classification	Clinical action
Isolated RBD	Prodromal manifestation (definitional)	Confirm by video-PSG; counsel; annual olfactory, motor and cognitive surveillance; offer trial enrolment
Insomnia (frequent/chronic)	Prodromal marker and probable aetiological factor	Treat per guideline on established grounds; do not present as PD prevention
EDS / objective napping	Predominantly prodromal	Incorporate in prodromal risk calculation (LR+ 2.7); prefer objective measurement; treat reversible contributors
Circadian amplitude loss	Predominantly prodromal	Research tool; not yet a clinical test
EEG slowing (low α/θ)	Prodromal (subclinical neurodegeneration)	Candidate marker for formal LR evaluation
Obstructive sleep apnoea	Neither established	Treat for standard indications; no PD risk counselling
Restless legs syndrome	Neither established	Examine to exclude early parkinsonism; no risk counselling
Long sleep duration	Reverse causation	No action

DISCUSSION

This synthesis finds it more appropriate to assume a graded rather than uniform relationship, from the standpoint that both the effects and the causal position of disorders vary. iRBD is NOT a risk factor for PD, it's an early symptom of the same disease. Its LR+ of 130 ^[7], 6.25% annual conversion ^[8], cumulative risk >90% at 14 years ^[9,10] and autopsy-confirmed Lewy pathology ^[10] is what the Braak framework predicts: the sublateralodorsal neurons and targets in the ventromedial medulla underpinning REM atonia lie at stages 1-2, caudal to the nigra ^[5], and impairment of these neurons experimentally reproduces RBD ^[33].

Insomnia is at the other end of it, and is the only sleep disorder with a plausible aetiological claim. The argument is not about effect size, which is modest.

It is about convergence across a series of designs that each have particular biases. These include dose–response, persistence beyond 20 years, an E-value >2.4, robustness to mood and hypnotic adjustment, concordant polygenic score, and largest effect in youngest participants ^[11]. This fits with mechanistically, chronic insomnia is a hyperarousal state in which there is hypothalamic–pituitary–adrenal over activity ^[34] and a reduction in slow-wave sleep, which is the stage of maximal glymphatic clearance ^[30,31]; impaired clearance of extracellular α -synuclein, exacerbated by oxidative stress and neuroinflammation, likely promotes aggregation ^[32].

The counter-evidence should be taken equal. The Mendelian randomisation consistently fails to detect a causal effect of any sleep trait for PD ^[28,29] and this is quite a contrast to the polygenetic finding (which could



be due to selection bias from competing risks in Mendelian randomisation for late onset disease and/or under-powered instruments of 13–48 variants or alternatively to pleiotropy in a million variants score). Competing risk is another obstacle to translation; in a Fine–Gray model, the cause-specific IRR (1.54, 1.11–1.43) decreased because insomnia also predicted death^[11,45], meaning that insomnia could not be treated to reduce population PD incidence because insomnia is associated with competing mortality. Treatment is still warranted on sound bases^[47] but not for PD prevention. We emphasize that the range of pooled HR across the claims databases in the OSA literature^[14,15] is quite similar to the inverse cross-sectional estimate^[16] and that polysomnographic observation was negative in a population cohort (25) as well as in iRBD (8). Coded OSA has more clinical contact, and clinically diagnosed PD (1.63 to 1.18) demonstrates the confounding structure^[12]. The same can be said for RLS, which have a significant registry association, equating to approximately 18 days difference in time to diagnosis^[20,21].

This review differs from previous reviews in three ways: Firstly, the previous reviews combined prevalence with incidence, losing the OSA paradox; secondly, the previous reviews combined questionnaire-defined RBD with polysomnography-confirmed RBD, masking the 46-fold likelihood-ratio difference; and thirdly, the prevalence synthesis reported I^2 , but not prediction intervals, which revealed the poor information content of the pooled estimate^[17]. A further candidate marker not included in the MDS criteria is non-REM α/θ slowing, with the lowest quartile OR of 3.71^[25], which is higher than all other markers identified except RBD and dopaminergic imaging.

STRENGTHS AND LIMITATIONS

Strengths include large registry and biobank cohorts with complete follow-up, including one cohort with a mean follow-up of 24.6 years and 2,679 events; standardized polysomnography, actigraphy and quantitative electroencephalography; and autopsy verification.

Limitations are primarily structural. Only one study had sufficiently long follow-up to distinguish causation from prodromal effects, and it assessed insomnia using a single item. Associations weakened with longer follow-up, with the strongest effects observed over shorter

periods. Claims-based cohorts may have substantial exposure misclassification, while residual confounding by obesity, cardiometabolic disease, depression and medications remains possible; treatment-related confounding may also affect RLS findings. Generalisability is limited because most objective evidence comes from elderly White or Japanese-American populations; iRBD cohorts were 82.5% male and largely tertiary-referral based, while the second-highest-burden world region contributed no primary evidence. Finally, effect measures were not force-pooled because their comparability was uncertain.

CLINICAL IMPLICATIONS

In older adults, sleep paralysis warrants consideration of video polysomnography, particularly when iRBD is suspected. Confirmed iRBD carries an estimated risk of approximately 6% annually and 60% over 10 years; MDS criteria should guide risk stratification. In primary care, insomnia, excessive daytime sleepiness and napping are individually low-likelihood-ratio markers (≤ 2.7) and have limited value alone, although they are inexpensive and readily identifiable from routine records years before diagnosis. Wearable actigraphy may outperform subjective sleepiness for scalable screening, particularly for objective napping. Currently, iRBD cohorts provide the strongest opportunity for evaluating neuroprotective interventions, whereas OSA and RLS should not be treated specifically for PD prevention.

CONCLUSIONS

Sleep dysfunctions are heterogeneous and have variable associations with PD. In iRBD, there is high certainty that it represents a prodromal synucleinopathy, with polysomnography being the most sensitive clinical predictor. Evidence from long-latency insomnia, genetic studies, and dose–response relationships suggests a small contribution of insomnia to PD aetiology, except in frequent insomnia. Excessive daytime sleepiness, objective napping, reduced circadian amplitude, and electroencephalographic slowing are moderately informative prodromal markers, with two warranting consideration for inclusion in prodromal criteria. There is no convincing evidence that obstructive sleep apnoea, restless legs syndrome, or sleep duration initiate PD; observed associations may reflect surveillance bias, confounding, or reverse causation. Priorities include

objectively phenotyped cohorts with >20 years of follow-up, greater inclusion of women and underrepresented regions, and interventional studies evaluating whether treatment of sleep disruption can influence phenoconversion.

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