Review Article

The effects of deep brain stimulation on sleep: a systematic review and meta-analysis

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Abstract

Background: Deep brain stimulation (DBS) is a standard treatment for movement disorders, epilepsy, and others, yet its influence on postprocedural sleep quality remains an under-researched topic.

Study Objectives: We performed a systematic review and meta-analysis of all DBS effects on sleep.

Methods: The use of preferred reporting items for systematic reviews and meta-analyses guidelines (PRISMA) was utilized. We extracted demographic data, disease type/duration, DBS target, stimulation laterality (unilateral vs bilateral), follow-up lengths, and sleep pre/post-op measurements with polysomnography or across four standard sleep scales. The Cochrane methodology for evaluating RCTs was employed using the risk of bias assessments, data synthesis, and statistical methods, including forest plots (risk ratio; M-H random effects; 95% CI).

Results: Sixty-three studies were included in the overall analysis, representing 3022 patients. In a subgroup meta-analysis of subthalamic nucleus (STN) DBS for Parkinson's disease (PD), patients showed significant sleep improvement at three but not 12 months postoperatively with PDSS, at 12 but not 3 months with Epworth sleep scale, and at 6 months with nonmotor symptom scale. Pittsburgh sleep quality index (PSQI) showed no significant improvement in sleep at any time. Bilateral DBS showed significantly more improvement than unilateral DBS in the PSQI at 6 but not 3 months. Polysomnography showed significant sleep improvement at 1 week but not at 3 or 6 months. Most studies showed no significant sleep improvement for globus pallidus internus, centromedian thalamus, and ventral intermediate nucleus DBS.

Conclusions: STN-DBS for PD likely improves sleep; however, significant standardization in sleep scale outcome reporting and follow-up time is needed to effectively determine the target-dependent effects of DBS surgery on sleep.

Key words: deep brain stimulation; sleep; movement disorders; subthalamic nucleus

Statement of Significance

Sleep disturbances are associated with adverse health outcomes such as functional decline, depression, and increased mortality risk, yet currently, there exists no clear analysis encompassing the breadth of sleep-related postoperative effects after deep brain stimulation (DBS). We sought to systematically evaluate the current scope of literature regarding the effects on sleep after DBS across various targets and diseases quantified through various sleep measurement scales. We performed meta-analyses of results across four major sleep scales, as well as polysomnography, to provide an objective understanding of outcomes reported in the literature. This provides the largest and most comprehensive review of the current studies on this topic, emphasizing the vast heterogeneity in sleep reporting methods across studies and analyzing optimal methods.

Deep brain stimulation (DBS) is a neuromodulatory treatment for movement disorders, epilepsy, obsessive-compulsive disorder (OCD), and other brain diseases when the response to standard medications is inadequate [1]. Although DBS has become a standard treatment over the past few decades, its influence on sleep is uncertain. Sleep disturbances are associated with adverse health outcomes such as functional decline, depression, and increased mortality risk [2]. Hence, it is clinically important to understand the positive or negative effects of DBS on sleep, and potential differences across diseases and targets.

Currently, there is no conclusive standard length of follow-up to measure sleep-related effects after DBS, as each study reports follow-up data differently, ranging from 1 week to 5 years [3, 4]. Additionally, studies targeting the same region for DBS and measuring sleep have had variations in outcomes, sometimes even conflicting evidence [5, 6]. These variations may be explained by considering individual risk factors for patients when measuring sleep-related outcomes.

While previous studies have explored the effects of DBS on sleep for specific indications, systematic reviews of sleep-related effects across different indications and targets tend to group together various scales or follow-up time points, which may skew some results [7]. Most of the current literature assessing sleep quality has focused solely on DBS of the subthalamic nucleus (STN) for Parkinson's disease (PD). Changes in sleep quality are less studied in DBS for other diseases (e.g. epilepsy, essential tremor) and targets (e.g. centromedian [CM], anterior [ANT], and ventral intermediate nucleus [Vim] thalamic nuclei).

Here, we aimed to systematically review studies of sleep outcomes after DBS across different indications and targets, using both objective (polysomnography) and patient-reported measures of sleep quality.

Materials and Methods

A systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [8]. This study protocol was registered in advance at PROSPERO (CRD42023492307).

Eligibility criteria

The inclusion criteria were primary human studies, both randomized and non-randomized, with any measure of sleep-related effects after DBS that were reported in English, Spanish, or Portuguese (based on the authors' abilities to interpret studies in such languages). Studies of any disease, DBS target, and patient age and sex were included. We excluded studies that were literature reviews, systematic reviews, meta-analyses, case reports, guidelines, and assessments.

Information sources and search strategy

We searched the Medline, Embase, and Web of Science databases using the following keywords: ("deep brain stimulation" or DBS) AND (sleep OR REM OR insomnia OR nocturnal OR asleep OR "sleep disturbances" OR "poor sleep efficiency" OR "sleep time" OR "sleep fragmentation" OR polysomnography OR PSG). The full search strategy was designed by two authors (AW, NP), and papers from January 1, 1962, to October 1, 2023 (Supplementary Material 1) were included. In addition, we performed a backward and forward citation analysis and used each database's "similar articles" feature to identify additional studies.

Selection process, data extraction, data items, and effect measures

Three authors (AW, ST, and MW) independently performed the title and abstract screening. AW retrieved the full texts for the remaining articles. Three authors (AW, ST, and MW) performed the full-text screening. In addition, AW performed the backward and forward citation analysis. Moreover, three authors (AW, ST, and MW) screened trial registries. All discrepancies were resolved by consensus. The screening and inclusion process is shown in Figure 1, and abstracts for which full-texts could not be located through an extensive search of the literature were also removed (Figure 1). Excluded articles and reasons for exclusion are listed in Supplementary Material 2.

Primary outcomes for the study included changes in the means of the Epworth sleep scale (ESS), Parkinson's disease sleep scale (PDSS), Pittsburgh sleep quality index (PSQI), and nonmotor symptom scale (NMSS) sleep subscore specifically (Table 1). The mean of the sleep efficiency pre- and postintervention was collected for polysomnography studies [13]. Secondary outcomes included qualitative descriptions of effects on sleep and significant polysomnography characteristics (e.g. sleep architecture, sleep latency, sleep staging, total sleep time, wake time after sleep, rapid eye movement latency) [13]. Data collected from the studies included sample size, mean age of patients, disease type, mean disease duration, target area, intervention type, DBS laterality, levodopa equivalent daily dosage (LEDD), and follow-up interval, in addition to the sleep scale measurements.

Synthesis methods

We performed a narrative synthesis of the study and intervention characteristics across different diseases. A random effects model meta-analysis was performed to estimate each sleep scale's mean difference (MD) and corresponding 95% CIs. Standardized MDs were not used because the scales varied in direction, with some indicating improvement through higher scores while others reflecting improvement with lower scores. Heterogeneity was evaluated by employing the I^2 statistic, gauging the proportion of total variability among studies attributable to true differences rather than random factors. We deemed overall meta-analysis heterogeneity low when the I^2 value was less than 35% [14]. A sensitivity analysis was also performed to determine whether the overall study outcomes were significantly influenced by excluding a single study with a high to moderate risk of bias, using a one-study-removed methodology [15]. In addition, the *E*-value, a measure of the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to explain away a specific association, was calculated for all the significant estimates of the meta-analysis to understand the effect of possible unmeasured confounders [16, 17]. For this calculation, the estimates were first converted into standardized MDs and then input into an online *E*-value calculator [18].

Quality assessment and certainty of evidence

For quality assessment, we used the risk of bias 2 assessment tool (RoB 2) for the assessment of randomized clinical trials and the risk of bias in nonrandomized studies of interventions (ROBINS-I) tool for nonrandomized studies of interventions to assess the risk of bias for studies included in the meta-analysis [19, 20]. The RoB 2 is structured into five domains of bias, each focusing on a different aspect of trial design, conduct, and reporting and involving its own set of questions [19]. Similarly, the ROBINS-I tool evaluates the
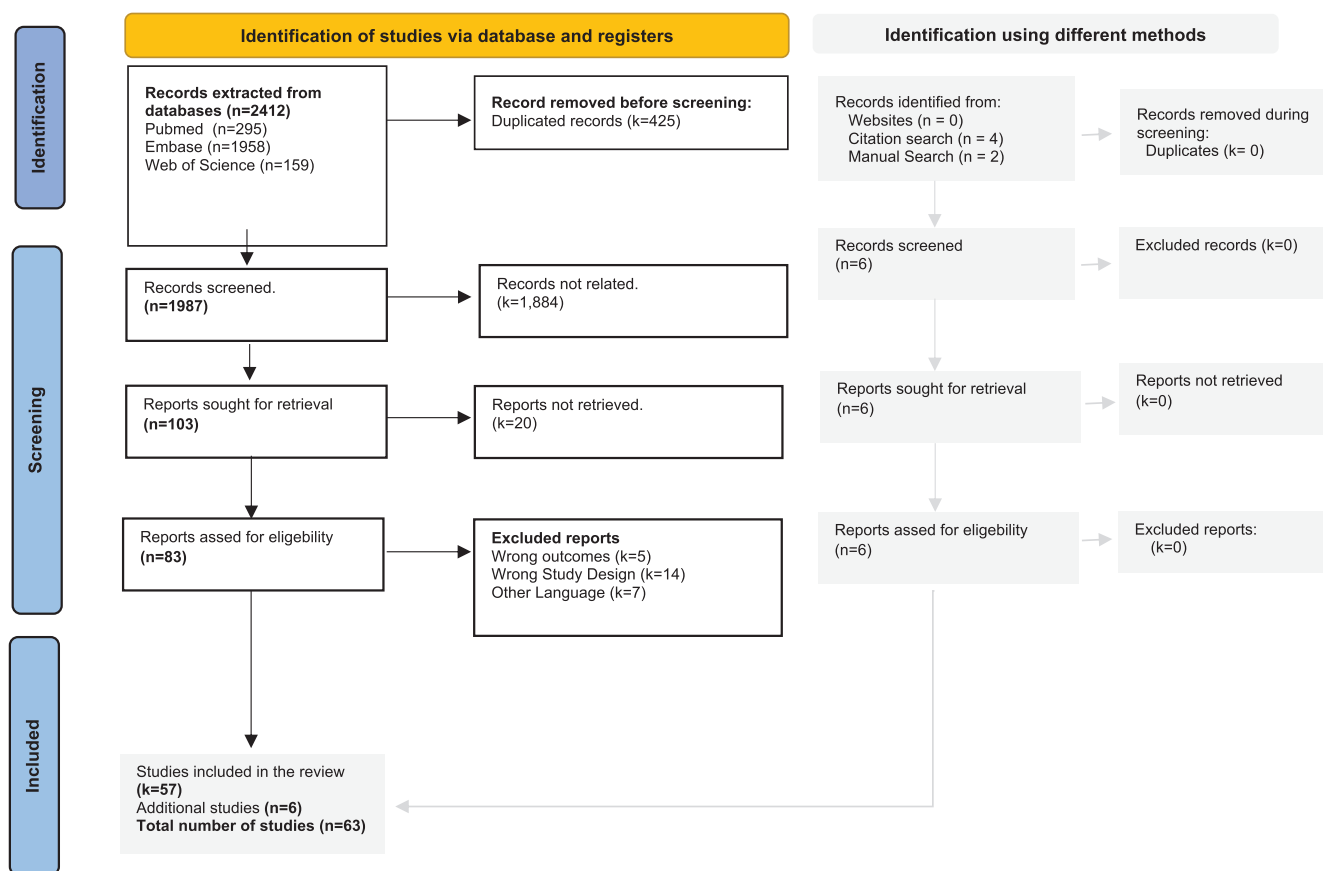
Figure 1. PRISMA screening flowchart.

Table 1. Sleep Scales Considered for Measuring Outcomes

Sleep scale	Functionality
Epworth sleepiness scale (ESS)	8-item rating scale assessing likelihood of sleeping (0–3) during 8 daily activities. Scores range from 0 to 24; higher score indicates worse daytime sleepiness. A score of 11–24 suggests excessive daytime sleepiness [9].
Nonmotor symptom scale–domain 2: sleep (NMSS)	30-item rating scale assessing severity (0–3) and frequency (1–4) of nonmotor symptoms, including sleep/fatigue, in patients with PD [10]. Scores range from 0 to 360; higher score indicates worse sleep/fatigue.
Parkinson's disease sleep scale (PDSS)	15-item visual analogue scale assessing frequency (0–10) of symptoms associated with sleep disturbance [11]. Scores range from 0 to 150; lower score indicates worse sleep disturbance.
Pittsburgh sleep quality index (PSQI)	19-item, 7-component (0–3) questionnaire assessing sleep quality and daytime sleepiness [12]. Scores range from 0 to 21; higher score indicates worse sleep and daytime sleepiness.

risk of bias in nonrandomized studies of interventions across seven domains, considering the study design, conduct, and reporting [20].

To assess the certainty of evidence, we used the grading of recommendations, assessment, development, and evaluation (GRADE) methodology, which classifies the certainty of evidence as very low, low, moderate, or high [21]. It does so by evaluating four aspects: risk of bias, inconsistency, direct evidence, and imprecision to inform the certainty of the evidence obtained through a summary of findings table for each outcome. The GRADE assessment was performed using the GRADEpro virtual platform.

Results

Study selection, study characteristics and narrative synthesis of included studies

A total of 1987 studies were screened by title and abstract from which 83 articles were included for full-text review (Figure 1). Of those, 63 studies were identified to be included in the qualitative synthesis, representing a total of 3022 patients (Supplementary Material 3). The mean age of patients was 60.5 ± 8 years (mean ± SD), and 1339 were female (47%). The median follow-up time across studies was 6 months (range 1–12 months); most were prospective cohort studies (51%). The most common diseases were Parkinson's disease (77% of studies), followed by Meige syndrome (6.6% of studies), epilepsy (6.6% of studies), and OCD (4.9% of studies). Other diseases included essential tremor (1.6% of studies), depression (1.6% of studies), and cluster headaches (1.6% of studies).

Meta-analysis

We performed a meta-analysis on the 26 studies that satisfied our preregistered homogeneity criteria (Table 2). All studies were performed in patients with PD targeting the STN. Sleep scales varied in outcome reporting, as summarized earlier (Table 1).

Table 2. Study Characteristics of Meta-Analysis Studies

Study	Country/region	Sample size	Age (mean ± SD; years)	Disease	Disease duration (years)	Target area	Laterality	Sleep scale or measure	LEDD change from baseline (mg)	Follow-up duration (months)
Amara 2012 [22]	USA	53	60 ± 9.5	PD	11.6 ± 5.5	STN	Unilateral	PSQI	−261.8 (3 months) −291.5 (6 months)	3, 6
Amara 2017 [23]	USA	20	61.4 ± 8.85	PD	10.1 ± 4.18	STN	Unilateral/ bilateral	PSG	—	15
Bargiotas 2021 [24]	Switzerland	50	62.5 ± 8.2	PD	Not reported	STN	Bilateral	ESS	70% reduction	12
Bauman-Vogel 2017 [25]	Switzerland	50	61 ± 10	PD	12 ± 5	STN	Bilateral	PSG	−656	6
Bjerknes 2020 [26]	Norway	49	62	PD	11	STN	Bilateral	PDSS	−602 (3 months) −652 (12 months)	3, 12
Bjerknes 2021 [4]	Norway	54	63	PD	12	STN	Bilateral	PDSS	−615	3
Cicolin 2004 [27]	Italy	5	63.8 ± 3.3	PD	13.8 ± 4.9	STN	Bilateral	PSG	−894	3
Dafsari 2020_1 [5]	Europe	40	57.7 ± 10.8	PD	11.3 ± 5	STN	Bilateral	NMSS	−538	6
Dafsari 2020_2 [28]	Europe	73	61.9 ± 7.7	PD	10.4 ± 5	STN	Bilateral	NMSS	−462.4	6
Dulski 2022 [29]	Poland	15	59.2 ± 7.8	PD	11.4 ± 4.3	STN	Not reported	PSG	—	6
Fernández-Pajarín 2021 [30]	Spain	20	59.3 ± 6.4	PD	8.4 ± 3.6	STN	Bilateral	NMSS	−741.5	6
Hao 2020 [31]	China	22	57.9 ± 6.8	PD	5.5 ± 4.1	STN	Bilateral	PSQI	—	1, 3
Iranzo 2002 [32]	Spain	11	63.6 ± 7.8	PD	17.3 ± 9.1	STN	Bilateral	PSQI, PSG	65% reduction	6
Liu 2021 [6]	China	21	59.6 ± 9.4	PD	6.4 ± 6.1	STN	Bilateral	PSQI	—	12
Ma 2023 [33]	China	78	61.8 ± 8.6	PD	9.3 ± 3.8	STN	Bilateral	PSQI	−47.9	1
Merlino 2014 [3]	Italy	15	Not reported	PD	10.6 ± 3.8	STN	Bilateral	PSG	—	1 week
Monaca 2004 [34]	France	10	57.4 ± 5.2	PD	12.1 ± 2.6	STN	Bilateral	PSQI, PSG	−516	3
Nishida 2011 [35]	Japan	10	57.5	PD	12.3	STN	Bilateral	PSG	−327.7	1 week
Ouyang 2021 [36]	China	15	60.2 ± 6.9	PD	7.2 ± 4.4	STN	Bilateral	PSQI	—	12
Oner 2022 [37]	Turkey	26	43.35	PD	13.75 ± 5.35	STN	Bilateral	PSG	−203.7	8
Peppe 2012 [38]	Italy	5	62.8 ± 1.9	PD	11.8 ± 3	STN	Bilateral	ESS	−216.2	3, 12
Petry-Schmelzer 2019 [39]	Europe	91	62.7 ± 7.9	PD	9.9 ± 4.6	STN	Bilateral	NMSS	−449.9	6
Sousori 2021 left [40]	Switzerland	16	59.81 ± 2.56	PD	11.88 ± 0.98	STN	Unilateral	PSG	−701.9	6
Sousori 2021 right [40]	Switzerland	11	62.82 ± 2.56	PD	12.45 ± 1.63	STN	Unilateral	PSG	−650.1	6
Torun 2020 [41]	Turkey	8	53.6 ± 4.1	PD	13.4 ± 5.3	STN	Bilateral	ESS, PSQI, PSG	—	3
Tolleson 2016 [42]	USA	5	62 ± 7.18	PD	9.8 ± 3.96	GPi	Bilateral	PSG	−408.1	6

USA, United States of America; PD, Parkinson's disease; STN, subthalamic nucleus; GPi, globus pallidus internus; PSQI, Pittsburgh sleep quality index; ESS, Epworth sleepiness scale; NMSS, nonmotor symptom scale–domain 2: sleep; PSG, polysomnography; LEDD, levodopa equivalent daily dosage.

Additionally, levodopa equivalent daily dose (LEDD) data was available and analyzed for 19 out of 26 (73.1%) of the available studies (Table 2). A summary of significant changes across sleep scales was also provided (Figure 2).

Significant improvement in sleep score was observed with the PDSS scale at 3 months (Figure 3), with a 26.44 MD in the pre- and postintervention score (95% CI [4.21; 48.66]). However, this score improvement was not seen at 12 months, showing an estimate of 27.14 (95% CI [-0.30; 54.57]) (Figure 3). Regarding the ESS scale, there was no statistically significant score improvement seen at

3 months (estimate −3.70 points; 95% CI [−8.01; 0.61]), however, it was seen at 12 months (estimate −3.92 points; 95% CI [−70.5; −0.79]) (Figure 4). In relation to the NMSS scale, there was a significant improvement in the score at 6 months (estimate −6.34 points; 95% CI [−7.63; −5.05]) (Figure 5). Furthermore, the PSQI scale showed no significant score improvement in sleep at 1 (estimate −1.05 points; 95% CI [−2.26; 0.16]), 3 (estimate −1.57 points; 95% CI [−3.72; 0.59]), 6 (estimate −3.87; 95% CI [−8.99; 1.25]), or 12 months (estimate −2.55 points; 95% CI [−6.31; 1.20]) time points (Figure 6, A). Finally, the polysomnography sleep efficiency

showed a significant improvement at 1 week (estimate 10.27; 95% CI [1.65; 18.90]; Figure 7), but not at 3 months (estimate 10.95; 95% CI [−2.95; 24.86]; Figure 7), or 6 months (estimate 2.18; 95% CI [−4.43; 8.78]; Figure 7).

In the subgroup analysis of unilateral vs bilateral STN-DBS for patients with PD, there was no significant difference seen in the PSQI score for unilateral (estimate −0.50 points; 95% CI [−2.01; 1.01]) vs bilateral DBS (estimate −2.33 points; 95% CI [−6.19; 1.53]) at 3 months ($p < .39$; Figure 6, B); however, there was a significant difference at 6 months (unilateral estimate −1.42 points; 95% CI [−3.46; 0.61] vs bilateral estimate −9.40 points; 95% CI [−13.20; −5.60]; $p < .01$; Figure 6, C). There was no significant subgroup
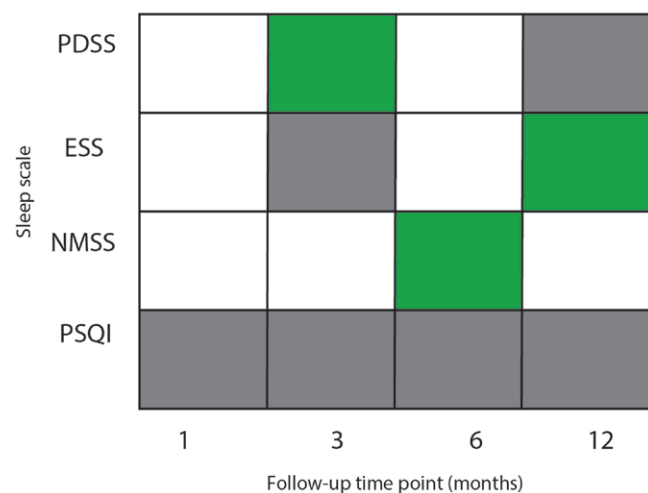
Figure 2. Summary of meta-analysis results. Various sleep scales and their improvement were measured at different time points. Green: significant sleep improvement shown; gray: no significant sleep improvement shown; white: analysis not able to be performed.

difference when comparing different time points across the sleep scales or polysomnography.

Sleep outcomes outside of STN-DBS

Several studies compared sleep improvement via various metrics depending on the target to determine the effect of DBS on sleep. For globus pallidus interna (GPi) stimulation, 78% of studies reported no significant change in sleep quality (Supplementary Material 3). For targeting the centromedian (CM) nucleus of the thalamus, only one of the studies observed an indirect change in EEG-sleep parameters after DBS, showing a persistence of the synchronization of interictal discharges during slow-wave sleep, a finding that indicates no effect of DBS stimulation on the sleep architecture of these patients [43]. Moreover, for ventral intermediate nucleus (Vim) DBS, only one study was found, reporting no significant change in sleep quality based on polysomnography recordings [44].

When comparing analyses by disease rather than by target, different patterns emerged. Out of the four studies that considered sleep quality changes after CM and ANT-DBS for patients with epilepsy, only one study reported improvement after ANT-DBS [45]. Similarly, only one out of four studies considering STN and GPi-DBS for Meige syndrome showed significant sleep quality improvement after bilateral STN-DBS (Supplementary Material 3) [36]. In those studies investigating sleep after DBS for depression, cluster headaches, and OCD, none clearly reported sleep improvements on a standardized scale [46–50]. The heterogeneous follow-up times (1–24 months) from these studies and lack of detailed reporting precluded using these reports in a quantitative analysis.

Risk of bias and certainty of evidence

The risk of bias was calculated for the 25 unique studies included in the quantitative analysis using the ROBINS-I scale primarily (Table 3). Twenty-one studies showed a low risk of bias, three
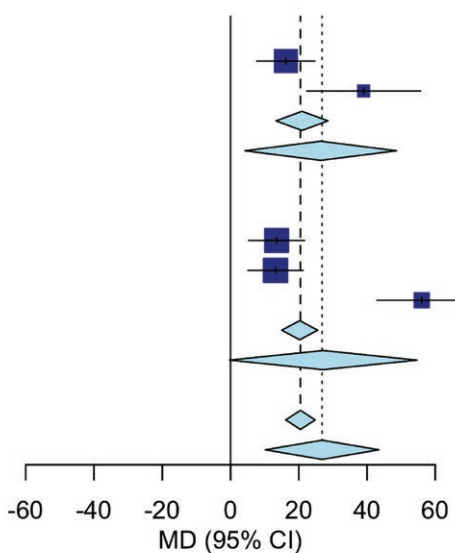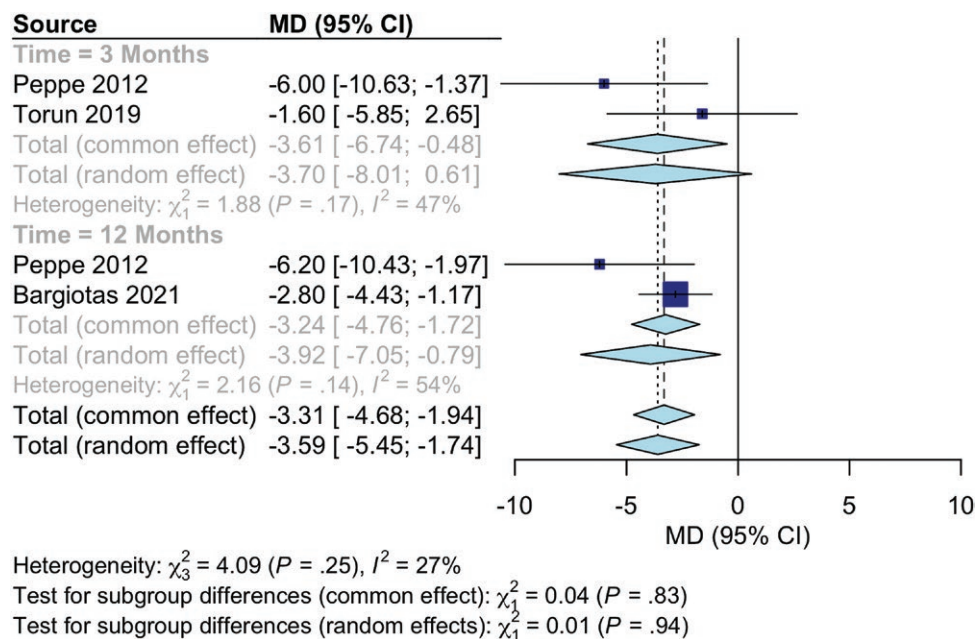

Figure 3. PDSS meta-analysis at 3 and 12 months.

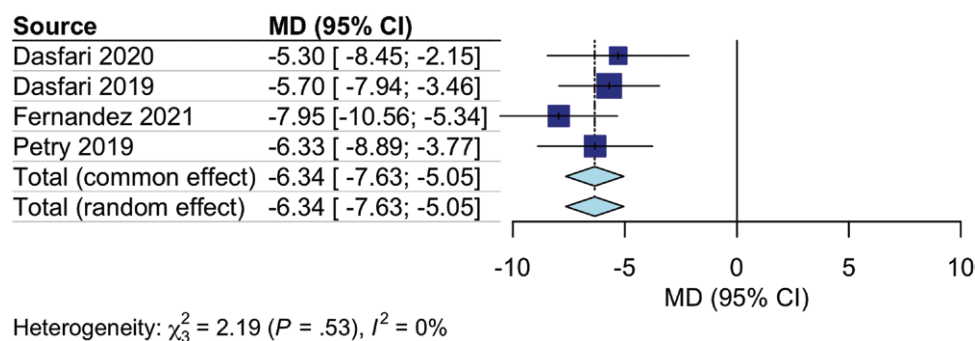**Figure 4.** ESS meta-analysis at 3 and 12 months.

Figure 5. NMSS meta-analysis at 6 months.

studies showed a moderate risk of bias, and only one showed a serious risk of bias. The serious risk of bias for the one study stemmed from bias in the selection of reported results.

The certainty of evidence was evaluated through the following risk factors: study design, risk of bias, inconsistency, indirectness, imprecision, and other possible confounders. Overall, the certainty of evidence was very low, reflecting the cumulative quality of the data of included studies (Table 4).

Sensitivity analysis

For the meta-analysis of the PSQI scale reported at 12 months, we excluded the highest-risk study, and no significance was seen regarding score improvement (estimate −0.76 points; 95% CI [−2.70; 1.18]) [36]. We calculated the E-value for the significant estimates (PDSS at 3 months, ESS at 12 months, NMSS at 6 months, and polysomnography sleep efficiency at 1 week) with their respective estimates and CI (Supplementary Material 4).

Discussion

Rigorous research studying the impacts on sleep after DBS is rare. We aimed to address this gap through careful, systematic review and meta-analysis, incorporating techniques to assess bias and the quality of evidence these studies provide. Several factors to consider when interpreting our results include the characteristics that make up each sleep scale, the physiology of DBS targets, and the certainty of our analysis and of the evidence.

Sleep scales

ESS. The sleep scales considered in this study have been extensively studied and explained in the literature; however, a short synopsis is included (Table 1). The ESS showed a significant score improvement of −3.92 points at 12 months for STN-DBS in patients with PD. The minimal clinically important difference (MCID) for the ESS scale has been reported as −2 points, and the change in score observed in the meta-analysis exceeded that [51]. The ESS uses a larger and less specific time frame compared to other sleep scales, which may be why patients report better sleep throughout longer intervals. The time range across which patients report symptoms is at the physician's discretion, which may lead to a significant source of variation [9]. Furthermore, excessive daytime sleepiness and fatigue may be confounding factors that can be affected by DBS and partially intercepted by these questionnaires, convoluting the analysis of sleep itself that is trying to be obtained. Additionally, studies have shown higher
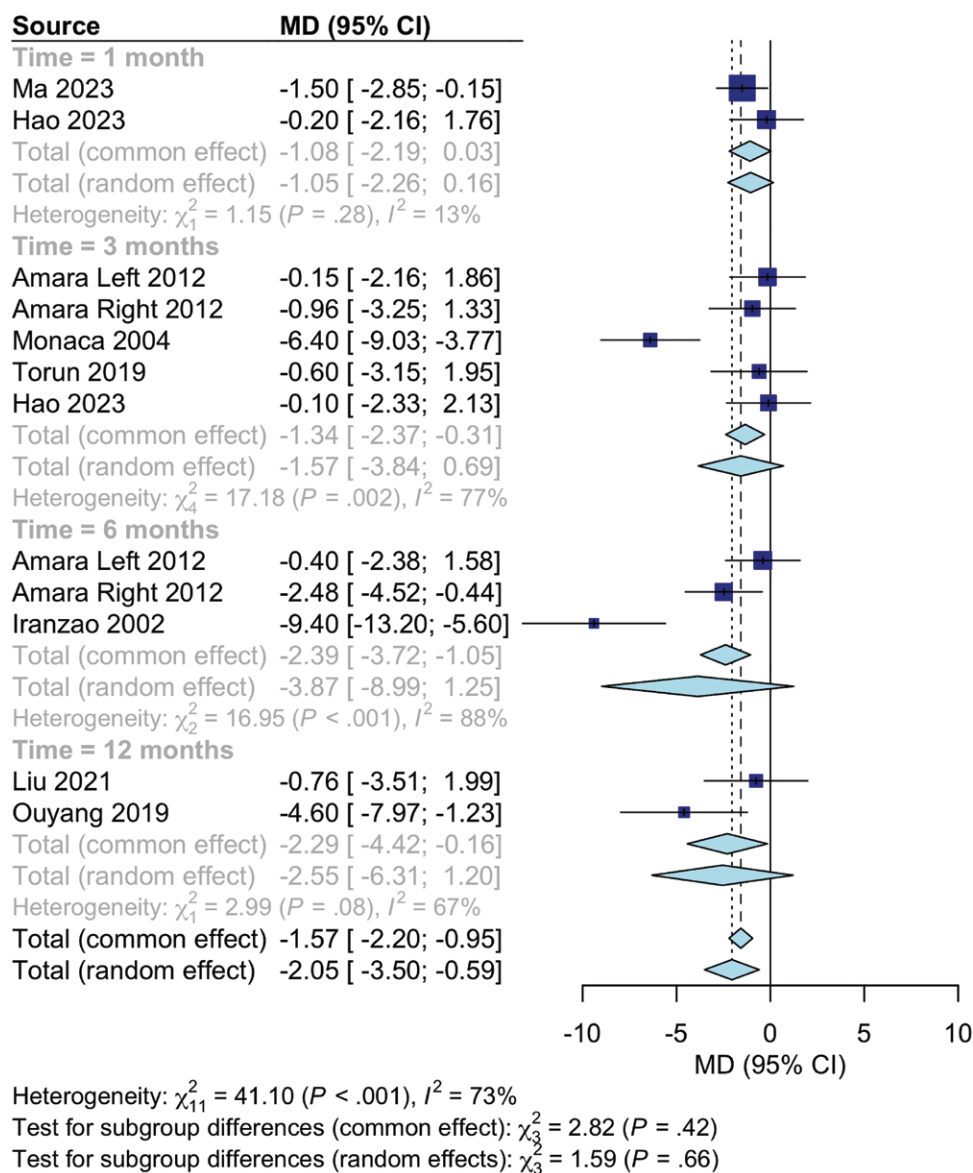
Figure 6. (A) PSQI meta-analysis at 1, 3, 6, and 12 months; (B) PSQI meta-analysis by stimulation laterality at 3 months; (C) PSQI meta-analysis by stimulation laterality at 6 months.

test–retest variability in clinical populations compared to the original validation study for the ESS, suggesting lower accuracy than originally thought for the ESS [52].

NMSS. Based on the meta-analysis, the NMSS-sleep subscore reported a significant improvement of –6.34 points in sleep quality at a 6-month time point. The MCID for the NMSS-sleep subscore has been reported to be around –4.3 points and 13.9 points for the overall scale [53]. The NMSS is specific to PD symptoms, which, for this meta-analysis, may offer a more accurate reflection of sleep quality. However, since the scale is a combination of daytime fatigue and restlessness associated with PD symptoms, it also does not directly measure nighttime sleep-related disturbances, which may be a point to consider in the interpretation of these results [10].

PDSS. In contrast to the ESS, the PDSS showed a significant sleep score improvement at 3 months but not 12 months for STN-DBS in patients with PD. Despite the statistical nonsignificance of PDSS improvement at 12 months, there was an overall tendency

towards long-term improvement. This scale is also specific to PD, compared to the ESS, which may apply to a broader spectrum of sleep quality changes. Possible explanations for short-term improvement at 3 months could be the temporary placebo effects inducing feelings of improved sleep quality after surgery, microlesion effect (although less likely given it is rare for this effect to last more than 1 month), or confounding due to natural progression in sleep quality decline as an effect of PD [3, 54, 55]. However, there is dissonance between this finding and the results seen with the ESS. An additional factor that may influence the measurement of sleep quality for PDSS is that the symptoms are measured over a 1-week time range. Although this provides more temporal specificity than the ESS, 1 week may still not be enough of a range to capture a representative average of sleep quality. Another limitation to note about this analysis is that no MCID could be found reported in the literature for this scale, primarily due to the PDSS being replaced by a more updated PDSS-2 scale in more recent studies [56].
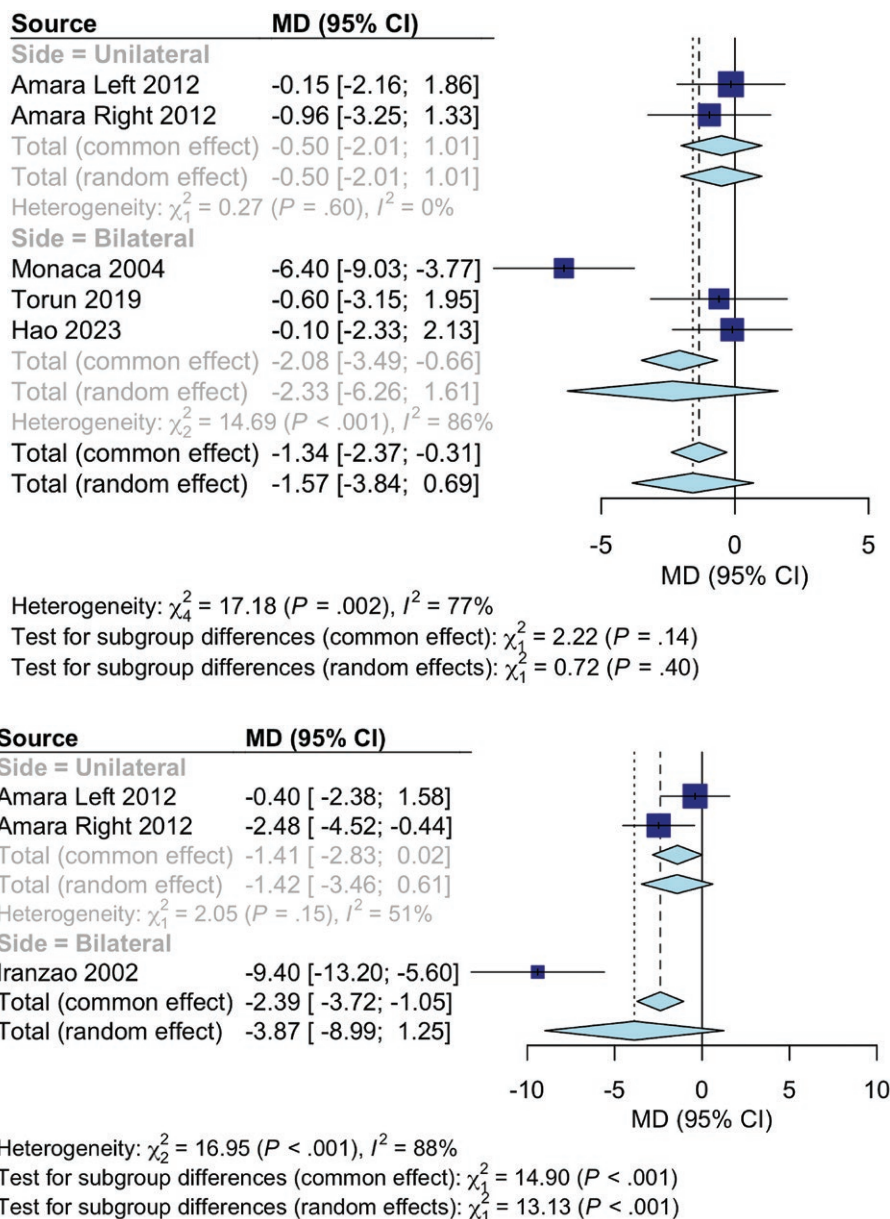
Figure 6. Continued

PSQI. Lastly, the PSQI showed no significant improvement in sleep quality for STN-DBS in PD at any time point measured. This finding was initially surprising, given that several individual studies reported significant improvements in sleep quality. However, significant heterogeneity was found in the reporting of results for these studies. Even after a sensitivity analysis, the meta-analysis did not show improvement at any time point using this scale. The MCID for PSQI has been reported as 4.4 points, and none of the time points measured showed a difference greater than this [57].

Additionally, three studies included in the meta-analysis for the PSQI posed risks of biases. At the 1-month time point, both studies included were of moderate risk of bias, potentially limiting the conclusions able to be made from the data. For example, one study posed a moderate risk of bias at the 3-month time point, reporting greater score improvement than the other studies in that subgroup, so accounting for that risk may imply that there is less score improvement at the PSQI at 3 months than reflected in the study average. The same idea is seen in

another study at 3 months with the PSQI, and one at 12 months with the PSQI [32, 36]. When interpreting these biases, if we account for the higher bias studies skewing the results of the meta-analysis, the PSQI presents even less certain significance of showing sleep improvement at any time point, making the results of these studies even more concerning in regard to sleep changes.

A significant drawback of this scale is that the questions consist of a combination of Likert-scale-like and open-ended questions. The combination of the question styles in determining a quantitative value for the scale may lead to variations in interpretation. Additionally, the longer time frame of 1 month for PSQI relies on recall memory, which could introduce recall bias among patients [58]. Furthermore, the PSQI is a more generic sleep outcome scale compared to the PDSS when it comes to patients with PD specifically. When comparing PSQI and ESS scores in patients with indistinct polysomnographic outcomes, the scores were found to have a weak correlation since PSQI is more linked to
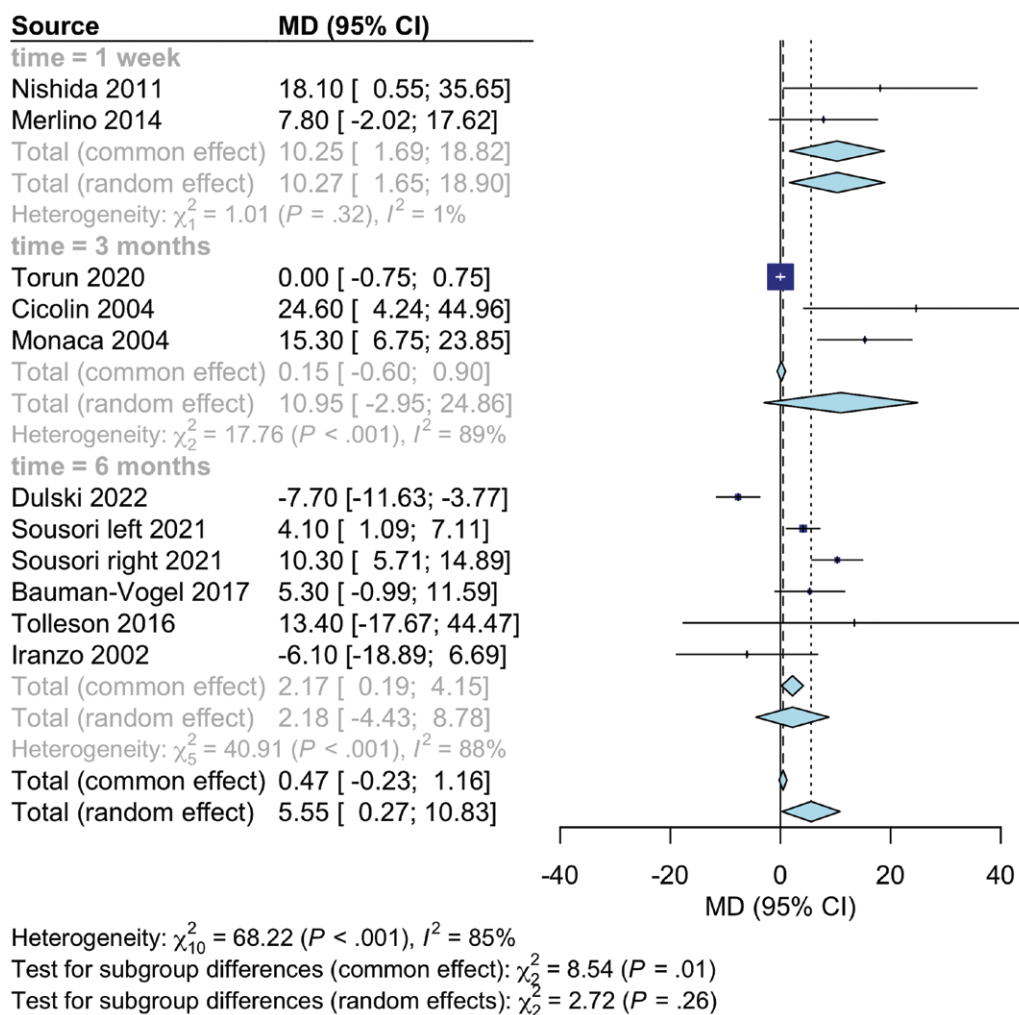
Figure 7. Polysomnography meta-analysis.

psychological symptom ratings [58]. This further supports the weak association between objective measures like polysomnography with PSQI and ESS [59, 60].

Polysomnography. When measuring sleep efficiency changes with polysomnography, we found significant differences showing sleep efficiency improvement in the first week but not at the 3- and 6-month time points. Polysomnography is the gold standard for measuring sleep improvement, and our results suggest that the effect of DBS on sleep may diminish over time. This may be due to several reasons, including potential placebo effects or transient "microlesion" effects of the DBS surgery that resolve by the 3- or 6-month time points [3]. While it was attempted to perform a meta-analysis on a wider breadth of objective PSG characteristics, such as sleep architecture, sleep latency, sleep staging, total sleep time, and more, the only data that was able to be consistently found across DBS-related studies was the metric for sleep efficiency. A larger number of studies investigating the effects on these more detailed PSG characteristics in patients at adequate pre- and post-DBS timepoints would serve greatly beneficial to elucidating the most objective improvements in overall sleep metrics for patients after DBS surgery.

Progression of sleep disturbances. When interpreting the data across all sleep scales, it is also important to consider the natural progression of sleep-related changes occurring among patients with PD. Sleep disturbances due to the progressive development of PD,

have an incidence of around 90%, being one of the most prevalent nonmotor symptoms of the disease [55, 61]. A study by Tholfsen et al. demonstrated that although the prevalence of patients with PD who suffered from insomnia increased notably in the early stage (around 1 year) of the disease, the change tended to drop off at longer time points (around 5 years) [62]. However, these results may differ for other sleep-related disturbances, such as excessive daytime sleepiness and REM sleep behavior disorder [61]. Nonetheless, most studies investigating these changes track their effects over long-term time points, generally more than 1 year. Since all the studies included in our meta-analysis examined sleep changes at 12 months or less, our findings may be more attributable to the immediate effects of DBS on sleep as opposed to longer-term effects resulting from natural PD progression.

Due to variability in the reporting of time points across qualitative studies considered and the meta-analysis, arriving at an optimal follow-up time at which to perform a postoperative sleep assessment was not able to be done confidently. This remains a question to be further investigated, requiring more randomized studies controlled for sleep scale, target area, and other demographics while comparing follow-up durations.

Effects of anti-Parkinsonian medications on sleep. One of the most important confounders to consider in the interpretation of sleep changes after DBS for PD is the impact of anti-Parkinsonian medications, such as levodopa, monoaminase oxidase B inhibitors,

Table 3. ROBINS-I Risk of Bias Assessment

ID	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall risk of bias
Amara 2012 [22]	Low	Low	Low	Low	Low	Low	Low	Low
Amara 2017 [23]	Low	Low	Low	Low	Low	Low	Low	Low
Bargiotas 2021 [24]	Low	Low	Low	Low	Low	Low	Low	Low
Bauman-Vogel [25] 2017	Low	Low	Low	Low	Low	Low	Low	Low
Bjerknes 2020 [26]	Low	Low	Low	Low	Low	Low	Low	Low
Bjerknes 2021 [4]	Low	Low	Low	Low	Low	Low	Low	Low
Cicolin 2004 [27]	Low	Low	Low	Low	Low	Low	Low	Low
Dafsari 2020_1 [5]	Low	Low	Low	Low	Low	Low	Low	Low
Dafsari 2020_2 [28]	Low	Low	Low	Low	Low	Low	Low	Low
Dulski 2022 [29]	Low	Low	Low	Low	Low	Low	Low	Low
Fernández-Pajarín 2021 [30]	Low	Low	Low	Low	Low	Low	Low	Low
Hao 2020 [31]	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Iranzo 2002 [32]	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Liu 2021 [6]	Low	Low	Low	Low	Low	Low	Low	Low
Ma 2023 [33]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Merlino 2014 [3]	Low	Low	Low	Low	Low	Low	Low	Low
monaca 2004 [34]	Low	Low	Low	Low	Low	Low	Low	Low
Nishida 2011 [35]	Low	Low	Low	Low	Low	Low	Low	Low
Ouyang 2021 [36]	Low	Low	Low	Low	Low	Low	Low	Low
Oner 2022 [37]	Low	Low	Low	Low	Low	Low	Serious	Serious
Peppe 2012 [38]	Low	Low	Low	Low	Low	Low	Low	Low
Petry-Schmelzer 2019 [39]	Low	Low	Low	Low	Low	Low	Low	Low
Sousori 2021 [40]	Low	Low	Low	Low	Low	Low	Low	Low
Torun 2020 [41]	Low	Low	Low	Low	Low	Low	Low	Low
Tolleson 2016 [42]	Low	Low	Low	Low	Low	Low	Low	Low

and more. Overall, the effects of levodopa and dopamine agonists (DAs) on sleep architecture in PD appear to be variable, influenced by factors such as disease duration, medication dosage, and the specific pharmacodynamic characteristics of the levodopa formulation or DA used [63]. Some studies have noted that increased LEDD was associated with increased wakefulness after sleep onset and REM latency and decreased total sleep time; however, conflicting evidence has been reported when the effects of levodopa and dopamine agonists (DAs) were evaluated separately [64, 65]. Nearly all studies analyzed in our meta-analyses solely reported LEDD rather than breakdowns of levodopa and DAs and did not conduct a multivariable analysis to adjust for this confounder. To

Table 4. GRADE Pro Assessment

№ of studies	Certainty assessment						Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of individuals	Mean difference (95% CI)		
At 3 months using PDSS										
2	Nonrandomized studies	Not serious	Serious*	Very serious†	Serious‡	All plausible residual confounding would reduce the demonstrated effect	54	26.44 per (4.1 to 48.66)	⊕○○○ Very low	Critical
At 12 months using PDSS										
3	Nonrandomized studies	Not serious	Serious*	Very serious†	Serious‡	All plausible residual confounding would reduce the demonstrated effect	108	27.14 per (−0.3 to 54.57)	⊕○○○ Very low	Critical
At 3 months using ESS										
2	Nonrandomized studies	Not serious	Not serious	Very serious†	Serious‡	All plausible residual confounding would reduce the demonstrated effect	13	−3.7 (−8.01 to 0.61)	⊕⊕○○ Low	Important
At 12 months using ESS										
2	Nonrandomized studies	Not serious	Not serious	Very serious†	Serious‡	All plausible residual confounding would reduce the demonstrated effect	55	−3.9 (−7.05 to −0.79)	⊕⊕○○ Low	Important
At 6 months using NMSS										
4	Nonrandomized studies	Not serious	Not serious	Very serious†	Serious‡	All plausible residual confounding would reduce the demonstrated effect	224	−19.3 (−24.32 to −14.3)	⊕⊕○○ Low	Important
At 1 month using PSQI										
2	Nonrandomized studies	Not serious	Serious*	Very serious†	Serious‡	All plausible residual confounding would reduce the demonstrated effect	78	−1.1 (−2.26 to 0.16)	⊕○○○ Very low	Important
At 3 months using PSQI										
5	Nonrandomized studies	Serious§	Serious*	Very serious†	Not serious‡	All plausible residual confounding would reduce the demonstrated effect	71	−1.6 (−3.72 to 0.59)	⊕○○○ Very low	Important
At 6 months using PSQI										
3	Nonrandomized studies	Serious§	Serious*	Very serious†	Not serious	All plausible residual confounding would reduce the demonstrated effect	64	−3.9 (−8.99 to 1.25)	⊕○○○ Very low	Important
At 12 months using PSQI										
2	Nonrandomized studies	Serious§	Serious*	Very serious†	Serious‡	All plausible residual confounding would reduce the demonstrated effect	36	−2.6 (−6.37 to 1.15)	⊕○○○ Very low	Important
Using polysomnography										
10	Nonrandomized studies	Not serious	Serious*	Not serious	Serious‡	All plausible residual confounding would reduce the demonstrated effect	202	5.55 (0.27 to 10.83)	⊕⊕○○ Low	Important

*Poor overlap of CIs.
†The measurement of the outcome is through a self-reported scale. Due to the nature of the outcome, there is a strong possibility of recall bias.
‡There are wide CIs.
§Some studies have a moderate risk of bias.

control for this, we calculated the E-value, which represents the minimum strength of association an unmeasured confounder would need to have with both the exposure and the outcome, in terms of standardized MDs, to explain away the observed associations. For instance, a confounder such as the effect of levodopa medication on sleep would need to change sleep efficiency by 3.08 points to fully explain away the observed effect of DBS on sleep efficiency. Even though, with the available evidence, it is not possible to account for the impact of this or other unmeasured confounders, it gives an approximation of how strong the impact should be to explain away the associations we found.

It is important to mention that a reduction in LEDD, naturally due to the regression of Parkinsonian symptoms with the DBS procedure, should lead to a further amelioration of negative sleep symptoms. However, even with these significantly notable LEDD reductions that may be confounding the effect of DBS-related sleep changes, we still struggle to conclude a clear, significant improvement in sleep efficiency over time through the results of the meta-analysis. To truly determine the direct effects of DBS on sleep, studies with patients free of anti-Parkinsonian medications for a certain preoperative period to wean off the LEDD-related effects on sleep would be most beneficial.

Sleep physiology

The STN is hypothesized to play a role in sleep-wake regulation [25]. The nucleus has inhibitory connections with the anterior hypothalamus and the upper section of the mesencephalic reticular formation. Additionally, it provides glutamatergic innervations to the substantia nigra pars compacta which, in turn, projects to various brain regions associated with the regulation of sleep [25]. Additionally, the pedunculopontine nucleus (PPN) has been linked to wakefulness and REM modulation. In patients with PD, low-frequency PPN-DBS has been suggested to ameliorate nighttime sleep issues and daytime sleepiness [66, 67]. Interestingly, the STN has reciprocal connections with the PPN. In PD, heightened inhibitory input from the basal ganglia to brainstem nuclei may lead to a reduction in excitability of the PPN and brainstem [66, 67]. This diminished excitability may potentially be alleviated by STN-DBS. The application of STN and substantia nigra pars reticulata DBS (STN + SNr-DBS) has been posed to be advantageous in mitigating sleep disturbances in PD by modifying the activity of the basal ganglia-brainstem projection through a release of the pathological inhibition of the pedunculopontine nucleus, a pathological state that is usually present in people with abnormal sleep [67, 68]. The potential positive effects of combined STN and substantia nigra pars reticulata DBS (STN + SNr-DBS) on sleep are grounded in the hypothesis that there is an alteration in the modulation of basal ganglia-brainstem projections [67, 68]. This alteration is thought to result from the release of pathological inhibition on brainstem centers like the PPN and locus coeruleus, which play pivotal roles in sleep-wake cycles [67, 68].

However, only one study was found that investigated the role of STN + SNr-DBS, comparing sleep-related outcomes of STN + SNr-DBS to a more conventional STN-DBS [67]. Hidding et al. found that for general sleep quality symptoms in the PDSS-2, there was no significant difference between STN-DBS and STN + SNr-DBS. However, for improving restless leg syndrome (RLS) symptoms at night and immobility at night, combined STN + SNr-DBS seemed to be superior to STN-DBS. There was an overall lack of studies found from our analysis that studied the effects of DBS on

specific sleep disorders, making it difficult to perform any analyses shedding light on specific disorders.

Additional targets that were studied, like CM, GPi, and Vim, lacked sufficient data for formal meta-analysis but have been linked to sleep in other ways. In rodent models, the CM has been shown to play a role in controlling sleep and wakefulness, with a study by Gent et al. suggesting that CM neurons modulate brain-wide cortical activity during sleep [69]. The basal ganglia have been shown to contain pathways that directly modulate sleep-wake behaviors via a cortico-striato-pallidal loop, motivating studies on sleep in patients receiving GPi-DBS [70–72]. Similarly, the Vim is hypothesized to be involved in thalamic networks that may be responsible for sleep disorders [44].

Heterogeneity, risk of bias and certainty of evidence

Based on the GRADEpro analysis, the certainty of evidence was very low to low. This can be attributed to several reasons. First, there is a poor overlap of CIs, even though intervals are wide, due to widespread outcome reporting. Due to the nature of the outcome measured (sleep), it happens to be so through self-reported scales, and there is also a strong possibility of recall bias. Second, some studies showed moderate or serious risk of bias, further lowering the certainty. This was mostly due to patients losing to follow-up reporting or bias in the selection of reported results. Additionally, due to the nature of this review, which is trying to address a broad question, high heterogeneity can be expected. Meta-analyses addressing broadly framed questions or the incidence or prevalence of a phenomenon in diverse environments may assemble highly heterogeneous studies [73].

Limitations

Some limitations in this study merit attention. First, the considerable heterogeneity in outcome reporting observed across the included studies impedes the ability to conduct confident, unified analyses. This variability arises from differences in sleep scales, disease indications, DBS targets, and the timing of follow-up assessments, undermining data consistency. Certain scales more commonly reported and include sleep measures, such as the MDS-unified Parkinson's disease rating scale part 1, were not broken down with sufficient granularity to extract scores solely from the sleep-related sections and, hence, had to be foregone in the quantitative analysis. Second, the evidence suffers from indirectness attributable to the reliance on self-reported outcome measurement tools. Such instruments may not accurately reflect sleep outcomes, thereby limiting the comparability of reported sleep metrics. Moreover, a significant proportion of the studies designate sleep as a secondary, rather than primary, outcome measure. This prioritization could result in effect sizes that are sufficiently robust for primary outcomes but not for secondary outcomes related to sleep. Third, unmeasured confounders present challenges in data interpretation due to insufficient detail. For example, the effect of PD on sleep, individual sleep physiology variations, and the effect of PD medication on sleep are variables that can be associated with the exposure and outcomes, changing the direction of the estimates and complicating the isolation of the intervention's impact. Additionally, specifying certain associated sleep disorders such as RLS or REM behavior disorder that may help paint a better clinical picture of PD patients was not able to be taken into account.

Conclusion

The effects of DBS on sleep appear either neutral or, at best, modestly better, with most evidence of a benefit derived from patients receiving STN-DBS for PD. The results are highly variable depending on the sleep scale used (ESS, PDSS, PSQI, or NMS) and the timeframe during which the scale was administered. Many of these studies show a moderate or severe risk of bias, when analyzed with standardized quality assessments. Although individual studies have shown significant sleep improvements after STN-DBS with the PSQI scale, our meta-analysis found no significant change in sleep with the PSQI at any follow-up time. Thus, for measuring sleep-related outcomes after DBS specifically, the PSQI may not accurately represent outcomes, warranting further research. Additionally, the differing degrees of sleep improvement by follow-up time in outcome measures are notable. Depending on the representativeness of symptoms by each sleep scale, additional research into specific sleep-related symptoms meticulously tracked across time points is needed to deduce contributing factors to overall sleep improvement. Further trials with standardized outcome reporting are needed to effectively determine the follow-up duration at which it is beneficial to measure sleep changes after DBS surgery.

Supplementary material

Supplementary material is available at *SLEEP Advances* online.

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The authors declare no conflict of interest.

Author Contributions

Aryan Wadhwa (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Software [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Niels Pacheco-Barrios (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Software [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Shreya Tripathy (Data curation [supporting], Formal analysis [supporting], Investigation [supporting], Methodology [supporting], Writing—review & editing [supporting]), Rohan Jha (Data curation [supporting], Formal analysis [supporting], Investigation [supporting], Methodology [supporting], Writing—original draft [supporting], Writing—review & editing [supporting]), Millen Wadhwa (Data curation [supporting], Formal analysis [supporting], Investigation [supporting], Methodology [supporting], Writing—review & editing [supporting]), Aaron Warren (Conceptualization [supporting], Investigation [supporting], Project administration [supporting], Supervision [supporting], Writing—original draft [supporting], Writing—review & editing [supporting]), Lan Luo (Project administration [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), and John D. Rolston (Conceptualization [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal])

Data Availability

All data from this study are publicly available through the references mentioned.

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