



REVIEW ARTICLE

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Efficacy of sleep interventions on postoperative delirium: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Sleep disturbances are risk factors for postoperative delirium (POD), and sleep interventions have been proposed as potential preventive measures. However, the effectiveness of sleep interventions in preventing POD is uncertain. We performed a systematic literature search using the PubMed, Embase, and Cochrane Library databases from inception until December 24, 2022. We included randomized controlled trials on sleep interventions and POD in adult surgery patients. The screening of titles, abstracts, and full texts was performed independently by two reviewers. Another two reviewers independently performed the data extraction and assessed the risk of bias. Pooled-effect estimates were calculated with a random effect model. Our primary outcome was POD, which was assessed with the confusion assessment method (CAM), CAM for the intensive care unit (CAM-ICU), or other delirium assessment tools. We used trial sequential analysis to control for type I and II statistical errors. We also conducted prespecified subgroup analyses, according to the type of intervention, efficacy of the intervention on postoperative sleep, sample size, participant age, delirium assessment tool used, and the type of surgery. Data were obtained from 25 trials, including 4799 participants. Sleep interventions had a statistically significant difference in the incidence of POD (relative risk (RR) = 0.60; 95% confidence interval (CI), 0.46–0.77; $I^2 = 58\%$). Stratified analyses indicated that the beneficial effects of sleep interventions were evident in trials where the interventions promoted postoperative sleep (RR = 0.51; 95% CI, 0.36–0.71) as compared to trials that did not (RR = 1.01; 95% CI, 0.77–1.31) (p -value for interaction between subgroups = 0.004). Our primary analysis demonstrated that in adult patients following elective surgery, interventions that improved postoperative sleep, as compared to the standard care or placebo groups, were associated with a lower risk of POD. However, such evidences are limited by the heterogeneity among trials and the small sample sizes of some trials.

Keywords Postoperative delirium, Sleep disorder, Sleep disturbance, Perioperative

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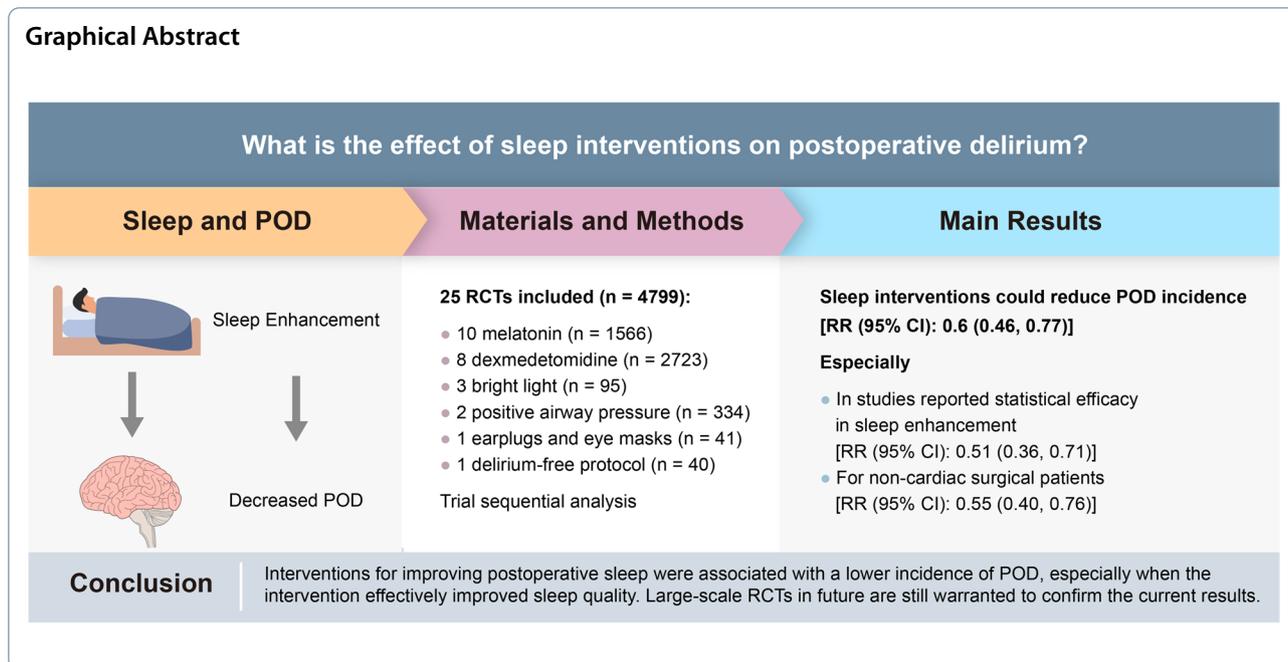
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Graphical Abstract



1 Introduction

Postoperative delirium (POD) is one of the most common complications after surgery [1]. As stated in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), clinical manifestations of POD include acutely occurring disturbances in attention, thinking, and cognition that fluctuate throughout the day [2, 3]. POD affects 11–51% of patients following major elective surgery and is associated with adverse consequences, such as prolonged hospital stay, increased healthcare costs, declined cognitive and physical function, and high morbidity and mortality [4–6]. Therefore, prevention of POD is essential to improve postoperative outcomes in patients. There are many predisposing and precipitating risk factors for POD, including increasing age, comorbidities, preexisting cognitive impairment, and sleep disorders [7, 8]. Some of these risk factors are modifiable, which could help in reducing the incidence and severity of POD.

The prevalence of preoperative sleep disturbances is in the range of 10–30% in healthy adults (aged > 18 years) and 36–43% in home-dwelling older adults (aged > 65 years) [9]. Sleep disturbances are also common during the perioperative period, which affects up to 40% of patients who undergo major inpatient surgeries [10]. The term “sleep disturbances” comprises multiple facets of sleep, including quantitative dimensions such as sleep duration and latency and qualitative

aspects such as depth or restfulness. Sleep disturbances are a combination of subjective complaints and objective evidences that include insomnia, obstructive sleep apnea, hypersomnolence, to name a few [11–13]. Perioperative sleep disturbances are associated with delayed postoperative recovery, higher incidence of POD or postoperative cognitive dysfunction, and poor quality of life [14, 15]. Previous studies also suggested that perioperative sleep disturbances are the main risk factors for POD [16–18]. Consequently, efforts were made to promote perioperative sleep to decrease the incidence of POD. Lower POD incidence has been reported after sleep interventions in some studies [19, 20] but not others [1, 21]. At the same time, meta-analyses on the reduction of the incidence of POD via sleep interventions have, thus far, focused exclusively on either pharmacological interventions or nonpharmacological interventions [22, 23] and hence, have not provided definite conclusions regarding the effect of comprehensive sleep interventions on the occurrence of POD.

Therefore, we performed an updated systematic review and meta-analysis to determine the pooled results and thus benefit clinical practice by synthesizing the available randomized controlled trials (RCTs) that assessed the efficacy of sleep interventions on preventing POD in adult surgical patients. We evaluated the existing body of research about the effects of sleep interventions on the incidence of POD.

2 Methods

We performed and reported this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see Supplementary 1) [24]. The protocol for this systematic review and meta-analysis was registered on INPLASY (<https://doi.org/10.37766/inplasy2023.1.0083>.) and is available in full on the www.inplasy.com (<https://doi.org/10.37766/inplasy00000000>).

2.1 Search strategy

A systematic search of literature was conducted from inception until December 24, 2022, using electronic databases (PubMed, Embase, and Cochrane Library). The detailed electronic search strategies for each database are illustrated in Supplementary 2. In addition, we searched Google Scholar for articles related to the extracted trials.

2.2 Inclusion and exclusion criteria

Two reviewers independently assessed the retrieved studies according to predetermined inclusion and exclusion criteria. Trials were included if they (1) were RCTs; (2) included patients undergoing elective surgery; (3) applied pharmacological or nonpharmacological interventions to alleviate perioperative sleep disturbances; and (4) clearly reported the incidence of POD. Trials were excluded if they (1) included patients aged < 18 years old; (2) were published as case series, systematic review and meta-analysis, protocol or conference paper; (3) had sleep interventions as part of a comprehensive program and the independent effect of sleep interventions cannot be derived; and (4) were published in a language other than English or Chinese.

The search results from all databases were entered into Endnote X9, duplicates were removed, and the remaining publications were screened for eligibility. The screening of titles, abstracts, and full texts was performed independently by two reviewers, using the same software. Ultimately, RCTs that met the inclusion criteria were included in the final analysis. Any discrepancies that emerged were addressed through a consensus-seeking process involving a third-party investigator.

2.3 Outcome measures

The outcome was the incidence of POD, which was assessed by delirium assessment tools, including DSM-5, Confusion Assessment Method (CAM), CAM for the intensive care unit (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), Neelon and Champagne (NEECHAM) Confusion Scale, and Nursing Delirium Screening Scale (Nu-DESC) [7].

2.4 Data extraction

Two reviewers independently utilized a predesigned data extraction form to collect key information from the trials, including the first author's name, publication year, country where the study was conducted, study design (single-center or multicenter trial), number of participants enrolled in each group, mean or median age of the participants, distribution of gender, type of surgery, intervention and comparative treatment, incidence of POD (outcome variable), measurement instrument employed to assess the occurrence of POD, and timepoint of the assessment. Any discrepancies that arose between the two reviewers were settled via discussion with a third author to ensure data accuracy and reliability.

2.5 Quality assessment of included studies

The risk of bias was assessed using the Cochrane Collaboration Risk of Bias Assessment tool [25], which covers seven domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Specifically, all these domains were evaluated, and each domain was assigned a risk classification of high, unclear, or low. Trials that exhibited one or more items associated with a high or an unclear risk of bias were ultimately classified as high risk [26]. To ensure the accuracy and reliability of the findings, any discrepancies that arose during risk assessment were resolved through careful discussion and, when necessary, by the involvement of a third-party investigator.

2.6 Data analysis

The statistical analyses were performed in RevMan (Review Manager version 5.4, Cochrane Collaboration, Oxford, United Kingdom) and R (R version 4.2.1 with the 'meta' package). Dichotomous outcomes were reported as the relative risk (RR) with 95% confidence interval (CI). Due to clinical and methodological heterogeneity among the trials, a conservative random-effects model was applied [27]. We identified statistical heterogeneity among included trials using the I^2 statistic and Mantel-Haenszel chi-square test (p -value for heterogeneity). Low, moderate, and substantial heterogeneities were indicated by $I^2 < 30\%$, $I^2 = 30\text{--}60\%$, and $I^2 = 60\text{--}90\%$, respectively. Similarly, $p > 0.10$ and $p < 0.10$ from the chi-square test denoted low and high heterogeneity, respectively [28]. The sources of heterogeneity were investigated in the following pre-specified subgroup analysis: (1) type of interventions (bright light, dexmedetomidine, melatonin, or positive

airway pressure), (2) efficacy of the interventions on postoperative sleep (positive, negative, or no evaluation), (3) sample size (< 100 or \geq 100), (4) age (< 65 years or \geq 65 years), (5) delirium assessment tool used (CAM/CAM-ICU, Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, NEECHAM, or other tools/not mentioned), (6) type of surgery (noncardiac surgery, cardiac surgery, or both cardiac and noncardiac surgery). Furthermore, for dexmedetomidine, the dose administered was different in intensive care unit (ICU) patients (sedative dose or low-dose) than in non-ICU patients (low-dose or mini-dose via a patient-controlled intravenous analgesia device). We also performed a stratified analysis of the two subgroups of patients to evaluate the association between the dosage of dexmedetomidine in the postoperative period and the incidence of POD. Sensitivity analyses were performed by removing articles one by one to assess the effect of individual trials on the overall results. Publication bias was evaluated by visually inspecting a funnel plot and formally testing by Peters' test. Two-sided statistical tests were performed, and an overall effect size with $p < 0.05$ indicated a significant difference.

We conducted a trial sequential analysis (TSA) using TSA software (version 0.9 beta, <http://www.ctu.dk/tsa>). The purpose of TSA is to adjust the statistical threshold

to minimize or eliminate the risk of type I and type II errors, which have been found to affect the results of meta-analyses [29]. The required information size (RIS) was determined based on the incidence of POD in the control group (21%) and a relative risk reduction of 28.57% in the experimental group [30] with a type I error of 5% (two-tailed) and type II error of 20% (80% power). TSA generated a graph that included a cumulative Z curve, a conventional meta-analysis boundary, the estimated RIS, and the trial sequential monitoring boundary (TSMB). If the cumulative Z curve crossed both the TSMB and the conventional meta-analysis boundary, and the number of recruited patients exceeded the RIS, the evidence was considered sufficient. Otherwise, the evidence was considered insufficient, which indicated that additional trials would be required [30, 31].

3 Results

3.1 Study selection

The processes of the search, screening, and selection of the trials are illustrated in Fig. 1. A total of 1267 records (1246 from the databases and 21 from other sources) were retrieved in the initial search. After removing duplicate trials (141 excluded), performing a screening of titles and abstracts (1064 excluded), and assessing the full texts (37 excluded), and assessing the full texts

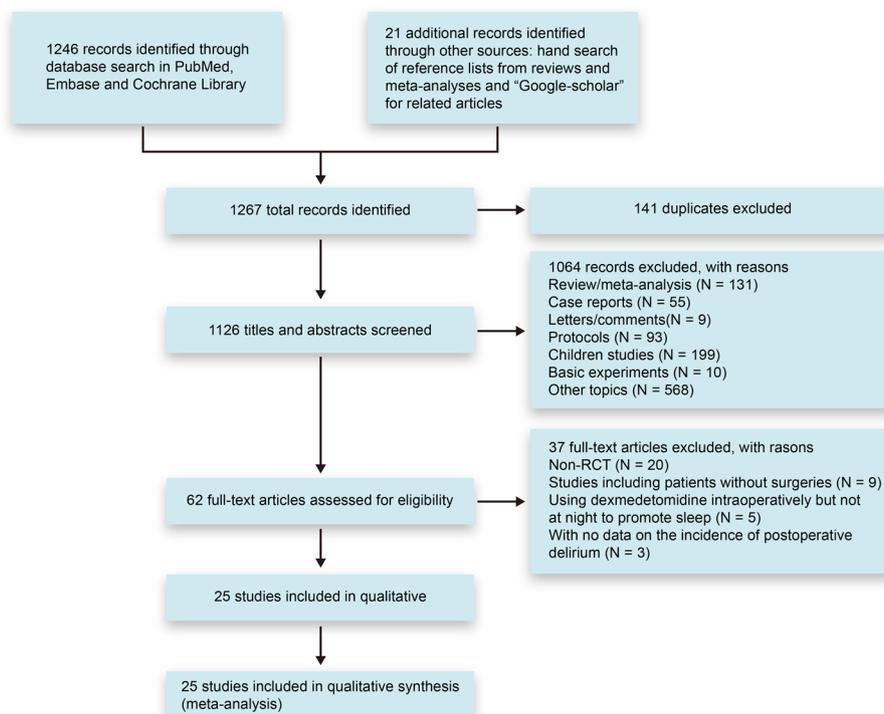


Fig. 1 Flow diagram of the literature search process. *RCT* Randomized controlled trial

(37 excluded), a total of 25 trials that met the inclusion criteria, including 4799 patients, were finally included in qualitative and quantitative analyses [1, 19–21, 32–52].

3.2 Study characteristics

The main characteristics of the included trials are described in detail in Table 1. These articles were published between 2007 and 2022. Among all included trials, ten trials evaluated the effect of melatonin [21, 37, 38, 41, 42, 44, 46, 48–50], eight assessed the effect of postoperative use of dexmedetomidine [1, 19, 20, 32, 33, 36, 47, 52], three evaluated the use of bright light in the morning [35, 39, 40], two included patients who were administered continuous positive airway pressure (CPAP) [43] or auto-titrating positive airway pressure (APAP) [34], and one used earplugs and eye masks to promote sleep-conducive environment [45]. Notably, the remaining one study used the delirium-free protocol (DFP), which involved an intramuscular injection of diazepam and a continuous intravenous infusion of flunitrazepam and pethidine [51]. Four trials enrolled patients underwent cardiac surgery [1, 44, 49, 50], nineteen trials included patients underwent noncardiac surgery [19–21, 32–37, 39–47, 51, 52], and the remaining two trials enrolled patients who underwent all type of surgeries [38, 48]. In a majority of the trials, the risk of POD was assessed using CAM or CAM-ICU [1, 19, 20, 32–34, 36, 38, 39, 43, 44, 46–49, 52], whereas three trials used the DSM criteria [21, 41, 51], two trials used the NEECHAM Confusion Scale [35, 40], and four trials used other tools or did not mention which tool was used [37, 42, 45, 50]. Nine trials reported statistical efficacy in improving sleep by interventions [19, 20, 36, 45, 47, 52], whereas five trials reported an insignificant effect of the sleep intervention on improvement of postoperative sleep quality [1, 33, 35, 38, 41]. The remaining eleven articles did not measure the efficacy of the intervention on postoperative sleep improvement [21, 32, 34, 37, 42–44, 46, 48, 49, 51].

3.3 Study quality

Many of the included trials were considered to have low risk of bias, given that they clearly reported random sequence generation (20 trials, 80%), allocation concealment (17 trials, 68%), blinding of personnel and participants (18 trials, 72%), blinding of the outcome assessment (22 trials, 88%), incomplete outcome data (0 trials, 0%), selective reporting (0 trials, 0%), and other bias (0 trials, 0%). Figure 2 presents a comprehensive depiction of the risk of bias in each study, as determined by the Cochrane criteria.

3.4 Pooled analysis

There was significant heterogeneity among the 25 trials ($p = 0.0001$; $I^2 = 58\%$). Meta-analysis using the

random-effects model demonstrated that interventions aimed at promoting postoperative sleep were associated with a reduced occurrence of POD compared with the control group. The pooled RR for POD was 0.60 (95% CI, 0.46–0.77; $p < 0.0001$) (Fig. 3). As demonstrated in Fig. 4, the RIS was 4002 participants. The number of recruited patients reached the RIS and the cumulative Z curve crossed the TSMB for benefit, indicating a statistically significant beneficial effect of the sleep interventions on POD.

3.5 Subgroup analysis

We explored heterogeneity with prespecified subgroup analyses (Supplementary Figs. 1, 2, 3, 4, 5, 6 and 7). The forest plot revealed significant difference in the POD incidence in trials investigating the effects of bright light therapy (RR=0.24; 95% CI, 0.09–0.65) or dexmedetomidine (RR=0.53; 95% CI, 0.39–0.72). However, the pooled results did not demonstrate a significantly low incidence of POD after melatonin administration (RR=0.79; 95% CI, 0.58–1.08) or positive airway pressure (PAP) therapy (RR=0.69; 95% CI, 0.13–3.82) (Supplementary Fig. 1). Regarding the efficacy of the sleep interventions on postoperative sleep, the subgroup analysis showed that the interventions that were effective in promoting postoperative sleep were also effective in preventing POD (RR=0.51; 95% CI, 0.36–0.71). Likewise, trials that did not assess perioperative sleep reported a reduction in POD risk among patients who received sleep interventions (RR=0.59; 95% CI, 0.39–0.91). However, the trials that did not find improvements in postoperative sleep among those receiving sleep interventions similarly did not report a reduction in POD incidence among study subjects (RR=1.01; 95% CI, 0.77–1.31) (Supplementary Fig. 2). Additional subgroup analyses were performed for different delirium assessment tools. Three trials used the DSM criteria (RR=0.83; 95% CI, 0.27–2.57), two trials used the NEECHAM criteria (RR=0.31; 95% CI, 0.07–1.31) for delirium assessment, both did not demonstrate a significant reduction in the incidence of POD. Sixteen trials used CAM or CAM-ICU (RR=0.61; 95% CI, 0.46–0.82) for the POD diagnosis, four trials used other tools or did not mention which tool was used (RR=0.34; 95% CI, 0.17–0.66) for the POD diagnosis, both subgroups demonstrated a comparable reduction in POD risk (Supplementary Fig. 3). Subgroup analyses also demonstrated significant difference in the POD incidence following noncardiac surgery (RR=0.55; 95% CI, 0.40–0.76) but not cardiac surgery (RR=0.68; 95% CI, 0.41–1.11) (Supplementary Fig. 4). There was a significant decrease in the incidence of POD by the sleep interventions, irrespective of the sample size, age, and dosage of dexmedetomidine (Supplementary Figs. 5, 6 and 7). We also performed a

Table 1 Main characteristics of all included studies

Study	Intervention	No. of patients	Country/center	Procedures	Age	Specific intervention in each group	Method of POD assessment and follow-up time	The incidence of POD	Sleep assessment tool and timepoint	Sleep promotion
Taguchi et al., 2007 [35]	Bright light	11	Japan/Single center	Surgery for oesophageal cancer	S: 56 ± 14 C: 59 ± 14	S: Light at 5000 lx was applied for 2 h in the morning, (5000lx 100cm) C: natural lighting environment after extubation. (600cm 1000 lx)	NEECHAM Confusion Scale POD 1-5	S: 1/6(16%) C: 2/5(40%) P=0.545	Accelerometer and memory heart rate recorder Started in the morning after admission to the ICU-removed after the beginning of ambulation (sampled every 5 min).	no
Ono et al., 2011 [40]	Bright light	22	Japan/Single center	oesophagectomy	S: 63.4 ± 9.7 C: 63.8 ± 7.8	S: Beginning at Day 2, 2 h bright light exposure starting at 7:30 a.m. for a total of four days. C: light conditions.	Japanese version of the NEECHAM Confusion Scale POD 1-6	S: 1/10(10%) C: 5/12(41.67%) P=0.162	Accelerometer and memory heart rate recorder After extubation- 1000 a.m. on Day 6 after surgery.	yes
Potharajoen et al., 2018 [39]	Bright light	62	Thailand/Single center	Abdominal Surgery, Thoracic Surgery, Orthopedic Surgery, Vascular Surgery	S: 68.1 ± 9.5 C: 68.3 ± 13.1	S: care as usual plus BLT (BLT consisting of 5,000 lux for 2 hours from 09:00-11:00, placed at a distance of 1.40 m from the patient's face) for 3 consecutive days. C: care as usual and was exposed to a light source of 500 lux.	CAM-ICU POD 1-5 Twice daily	S: 2/30(6.7%) C: 11/31(35.5%) P=0.006	ISI At 6:00 a.m., daily for three consecutive days following SICU admission.	yes
Sultan et al., 2010 [37]	Melatonin	102	Egypt/Single center	Hip arthroplasty	S: 70.4 ± 7.1 C: 72.3 ± 6.4	S: 5mg melatonin were given orally at sleep time at night of operation and 5mg melatonin 90 min before operative time. C: received nothing for sedation.	AMT POD 1-3	S: 5/53(9.43%) C: 16/49(32.65%) P=0.001	/	/
Nickkholgh et al., 2011 [42]	Melatonin	48	Germany/Single center	Major liver resection	S: 59 ± 10 C: 56 ± 11	S: a preoperative single center dose of melatonin (50 mg/kg BW) dissolved in 250 mL of milk was administered through the gastric tube after the intubation for general anesthesia. C: same amount of microcrystalline cellulose.	Unclear POD 1-7	S: 0/25(0) C: 1/23(4.34%) P=	/	/
de Jonghe et al., 2014 [21]	Melatonin	378	Netherlands/Multicenter	Acute hip surgery	S: 84.1 ± 8.0 C: 83.4 ± 7.5	S: melatonin 3 mg in the evening for 5 consecutive days, starting within 24 hours after admission. C: placebo	DSM-IV within 8 days of admission	S: 55/186 (29.6%) C: 49/192 (25.5%) P=0.378	/	/

Table 1 (continued)

Study	Intervention	No. of patients	Country/center	Procedures	Age	Specific intervention in each group	Method of POD assessment and follow-up time	The incidence of POD	Sleep assessment tool and timepoint	Sleep promotion
Robinson et al., 2014 [38]	Tryptophan	301	USA/Single center	Major elective operations	S:69±8 C:69±7	S: L-tryptophan, 1 g orally 3 times a day was started after surgery and continued for up to 3 days postoperatively. C: Placebo as L-tryptophan.	CAM-ICU and RASS Until discharge from the ICU daily	S:61/152(40%) C:55/149(37%) P=0.60	Average number of hours of sleep in the first 3 days after surgery.	no
Dianatkhan et al., 2015 [50]	Melatonin	137	Iran/Single center	Elective CABG	S:60.03±10.21 C:61.70±9.86	S: 3 mg of melatonin one hour before sleep time, from 3 days before surgery until the time of discharge. C: 10 mg of Oxazepam was given during the same periods.	Nursing records until the time of discharge	S:4/66(0.06%) C:9/71(0.12%) P=0.187	GSQS in the morning early after waking up, days -6, -5, +3 and +5	Yes
Ford et al., 2019 [49]	Melatonin	202	Australia/Multi-center	Major cardiac surgery	S:69±83 C:67.6±8	S: 7 days of treatment with melatonin 3 mg at night, starting 2 days before the surgery. C: Placebo	CAM POD 1-7 daily	S:21/98 (21.4%) C:21/104 (20.2%) Adjusted OR=0.78	/	/
Gupta et al., 2019 [48]	Ramelteon	100	India/Single center	Surgery at various surgical departments	S:69.30±4.05 C:70.64±3.76	S: one tablet of Ramelteon (8 mg) 12 hours before surgery and 1 tablet of Ramelteon (8 mg) 1 hour before surgery. C: placebo one tablet 12 hours before surgery and 1 tablet 1 hour before surgery.	CAM POD 1-3	S:2/50(4%) C:8/50(16%) P=0.307	/	/
Jaiswal et al., 2019 [46]	Ramelteon	117	USA/Single center	Elective pulmonary thromboembolism	S:58.1±14.1 C:56.1±15.8	S: Ramelteon 8 mg starting the night prior to surgery and for a maximum of six nights while in the ICU. C: placebo	CAM-ICU Assessments continued until discharge from ICU or through POD 8 if the patient remained in the ICU Twice daily	S:19/59(32%) C:22/58(38%) P=0.516	/	/
Oh et al., 2021 [41]	Ramelteon	71	USA/Single center	Elective primary or revision hip or knee replacement	S:74.3±5.5 C:75.4±5.0	S: an oral gel cap of ramelteon for 3 consecutive nights starting the night before surgery. C: placebo	DSM-V POD 0-2	S:3/33(9%) C:2/38(5%) P=0.79	RCSQ Night of surgery and postoperative day 1	no
Mahrose et al., 2021 [44]	Melatonin	110	Egypt/Single center	Coronary artery bypass graft surgery	S:67.0 ± 6.7 C:66.1 ± 6.3	S: oral melatonin tablet 5 mg the night before surgery and same dose was repeated every 24 hours for 3 postoperative days. C: without melatonin.	CAM-ICU POD 1-5 Twice daily	S:6/55(10.9%) C:15/55 (27.3%) P=0.029	/	/

Table 1 (continued)

Study	Intervention	No. of patients	Country/center	Procedures	Age	Specific intervention in each group	Method of POD assessment and follow-up time	The incidence of POD	Sleep assessment tool and timepoint	Sleep promotion
Yang et al., 2015 [33]	Dexmedetomidine	79	China/Single center	Free flap surgery	S:50.3 ± 15.0 C:50.6 ± 12.3	S: dexmedetomidine was given at a rate of 0.5 mg/kg/h for 1 hour before the operation was completed and continued in the PACU at 0.2 to 0.7 mg/kg continuously until the next morning. C: normal saline was given during the same periods.	CAM-ICU POD 1-5	S:2/39(5.1%) C:5/40 (12.5%) P=0.432	Patients were asked to rate their overall sleep quality (0 = worst, and 10 = best for sleep assessment) Within 5 days post-operatively	no
Guo et al., 2015 [32]	Dexmedetomidine	156	China/Single center	Radical surgery for oral cancer	S:71.9±5.1 C:70.7±4.6	S: dexmedetomidine 0.2µg/kg/h infusion for 12 h C: normal saline for 12 h	CAM-ICU POD 1-3 Twice daily	S:6/78 (7.7) C:21/78 (26.9) P < 0.01	/	/
Wu et al., 2016 [20]	Dexmedetomidine	76	China/Single center	Non-cardiac surgery	S:74±5 C:76±6	S: dexmedetomidine (continuous infusion at a rate of 0.1 µg/kg/h for 15 h) C: placebo	CAM POD 1-7 twice daily (at 8:00 am and 6:00 pm)	S:2/38 (5.3%) C:3/38 (7.9%) P=1	Polysomnogram during the period of study-drug infusion and NRS at 8:00 AM on the first, second, and third days after surgery.	yes
Su et al., 2016 [19]	Dexmedetomidine	700	China/Multi-center	Non-cardiac surgery	S:74.3±6.7 C:74.4±7.0	S: intravenous dexmedetomidine (0.1 µg/kg per h, from ICU admission on the day of surgery until 0800 h on POD 1) C: intravenous normal saline	CAM-ICU POD 1-7 Twice daily	S:32/350(9.1%) C:79/350(22.6%) P < 0.001	NRS At 0800 h on the first, second, and third days after surgery.	yes
Li et al., 2017 [1]	Dexmedetomidine	285	China/Multi-center	Elective coronary artery bypass graft and/or valve replacement surgery	S:66.4 ± 5.4 C:67.5 ± 5.3	S: dexmedetomidine was administered during anesthesia (0.6 ug/kg within 10 min followed by 0.4 ug/kg/h) and early postoperative period until the end of mechanical ventilation (0.1 ug/kg/h). C: normal saline was administered in the same rate for the same duration.	CAM/CAM-ICU POD 1-5 daily (from 8 to 10 am)	S:7/142(4.9%) C:11/143(7.7%) P=0.341	NRS POD 1-5 after the completion of daily delirium assessment	no
Wang et al., 2018 [52]	Dexmedetomidine	160	China/Single center	Knee arthroplasty	S:68.2±6.1 C:65.6±5.5	S: dexmedetomidine (0.1 µg/kg/h for 48 h after surgery) C: placebo	CAM-ICU POD 1-3 Daily	S:4/80 (5%) C:12/80(15%) P=0.035	NRS At 0800 h on the first, second, and third days after surgery.	yes

Table 1 (continued)

Study	Intervention	No. of patients	Country/center	Procedures	Age	Specific intervention in each group	Method of POD assessment and follow-up time	The incidence of POD	Sleep assessment tool and timepoint	Sleep promotion
Sun et al., 2019 [36]	Dexmedetomidine	557	China/Single center	Major elective non-cardiac surgery	S:68.0 (66.0–73.0) C:69.0 (65.0–74.0)	S: dexmedetomidine (0.1 µg/kg/h) immediately after surgery through patient-controlled intravenous analgesia device, and total continuous infusion time was 48 h. C: placebo (0.9% normal saline)	CAM-ICU/CAM POD 1–5 Twice daily	S:33/281(11.7%) C:38/276(13.8%) P=0.47	RCSQ During the first 3 postoperative days.	yes
Hong et al., 2021 [47]	Dexmedetomidine	710	China/Multi-center	Elective hip or knee arthroplasties, hip fracture repair or spinal surgery	S:71±5 C:71±5	S: dexmedetomidine (1.25 µg/mL) or placebo, for up to three days after surgery. C: placebo	CAM-ICU POD 1–5 Twice daily	S:17/356(4.8%) C:26/354(7.3%) P=0.151	NRS During the first 3 postoperative days, once daily, between 8–10 AM.	Yes
Le Guen et al., 2014 [45]	Earplugs and eye masks	41	France/Single center	Major non-cardiac surgery	S:62(3) C:59(3)	S: routine care plus eye mask and earplugs C: routine care for the first postoperative night	Postoperative disorientation For the first postoperative night (20:00 to 08:00)	S:0/20(0) C:3/21(14.3%) P=0.232	Spiegel scale, nurses' assessment and a wrist actigraphy During the first postoperative night in the PACU.	yes
Nadler et al., 2017 [43]	CPAP	114	USA/Single center	Elective knee or hip arthroplasty	S:65.1±8.4 C:66.3±9.4	S: Patients in the CPAP group were instructed to wear an auto-titrating positive airway pressure device any time they slept before surgery and any time they slept on postoperative days 0, 1 and 2. C: routine care	CAM POD 2	S:12/58(21%) C:9/56(16%) P=0.53	/	/
Wong et al., 2022 [34]	APAP	220	China/Multi-center	Elective hip or knee replacement	S:67.8±5.7 C:68.5±6.7	S: APAP for 72 h postoperatively or until discharge C: routine care after surgery	CAM POD 1–3 Twice daily	S:1/106 (0.9%) C:5/114(4.4%) P=0.21	/	/
Aizawa et al., 2002 [51]	DFP	40	Japan/Single center	Resection of either gastric or colon cancer through an open laparotomy	S:75.9±4.5 C:76.2±4.1	S: Diazepam (0.1mg/kg) was intramuscularly injected at 20:00h, and a continuous intravenous infusion of 0.04mg/kg of flunitrazepam, to maintain sleep, and 1mg/kg of pethidine, to maintain analgesia, was started at 20:00 h and continued for 8h. The same regimen was administered each night for the first three nights after surgery. C: received nothing.	DSM-IV POD 1–7 Twice a day	S:1/20(5%) C:7/20(35%) P=0.023	/	/

POD Postoperative delirium, NEECHAM Neelon and Champagne, BLT Bright light therapy, ISI Insomnia Severity Index, SICU Surgical intensive care unit, CAM Confusion Assessment Method, CAM-ICU CAM for the ICU, AMT Abbreviated Mental Test, DSM-IV the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, DSM-V the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, RASS Richmond Agitation and Sedation Scale, CPAP Continuous positive airway pressure, APAP Auto-titrating positive airway pressure, DFP Delirium-Free Protocol, CABG coronary artery bypass graft, GSQ5 Groningen Sleep Quality Score, RCSQ Richards-Campbell Sleep Questionnaire, NRS Numeric Rating Scale

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aizawa et al 2002	?	?	+	+	+	+	+
de Jonghe et al 2014	+	+	+	+	+	+	+
Dianatkah et al 2015	+	?	+	+	+	+	+
Ford et al 2019	+	+	+	+	+	+	+
Guo et al 2015	?	?	+	+	+	+	+
Gupta et al 2019	+	+	+	+	+	+	+
Hong et al 2021	+	+	+	+	+	+	+
Jaiswal et al 2019	+	+	+	+	+	+	+
Le Guen et al 2013	+	+	+	+	+	+	+
Li et al 2017	+	+	+	+	+	+	+
Mahrose et al 2021	?	?	?	?	+	+	+
Nadler et al 2017	+	?	+	+	+	+	+
Nickkholgh et al 2011	+	+	+	+	+	+	+
Oh et al 2021	+	+	+	+	+	+	+
Ono et al 2011	+	+	+	+	+	+	+
Potharajaroen et al 2018	+	+	+	+	+	+	+
Robinson et al 2014	+	+	+	+	+	+	+
Su et al 2016	+	+	+	+	+	+	+
Sultan et al 2010	+	+	+	+	+	+	+
Sun et al 2019	+	+	+	+	+	+	+
Taguchi et al 2007	?	?	+	+	+	+	+
Wang et al 2018	+	?	+	+	+	+	+
Wong et al 2022	+	+	+	+	+	+	+
Wu et al 2016	+	+	+	+	+	+	+
Yang et al 2015	+	+	+	+	+	+	+

Fig. 2 Risk of bias summary. Review of the author’s judgments about each risk of bias for each included study. Red indicates high risk, green indicates low risk, and yellow indicates unclear level of risk

post-hoc subgroup analysis according to the timepoint of administration of the interventions, whether preoperatively (RR=0.40; 95% CI, 0.17–0.90), postoperatively (RR=0.49; 95% CI, 0.34–0.71), or both (RR=0.92; 95% CI, 0.68–1.24) (Supplementary Fig. 8).

3.6 Sensitivity analysis

We used a one-by-one literature removal method to identify potential outlier trials responsible for the observed heterogeneity and to evaluate the stability of the results. We found no individual trials significantly reducing the heterogeneity after elimination. At the same time, we observed that no single study had a noteworthy impact on the pooled RR, which suggested that our meta-analysis results were robust (Fig. 5).

3.7 Publication bias

Publication bias was evaluated through visual examination of a funnel plot and formal testing by Peters’ test using R statistical software. The funnel plot for the overall incidence of POD showed no obvious asymmetry (Supplementary Fig. 9A and B). Additionally, Peters’ tests were conducted to further assess for publication bias, and no significant bias was found in this meta-analysis (p=0.1043) (Supplementary 3).

4 Discussion

We identified 25 RCTs with a total of 4799 participants that compared the incidence of POD between the sleep intervention group and the control group. Despite there was significant heterogeneity among the included trials, we showed that sleep interventions in surgical patients was associated with a decreased risk of POD. Notably, the reduction in POD risk was evident in trials that reported significant improvements in postoperative sleep. TSA confirmed the beneficial effect of sleep interventions. Leave-one-out meta-analysis demonstrated that our results were not driven by an individual study and further confirmed the robustness of the results.

According to the pooled results, we observed that the use of dexmedetomidine was associated with as high as a 50% reduction in the incidence of POD. Dexmedetomidine is a potent and highly selective agonist of the α2-adrenoceptor with analgesic, anxiolytic and sedative properties, which is widely used in clinical anesthesia and postoperative sedation [53, 54]. Previous studies have demonstrated that dexmedetomidine can induce nonrapid eye movement (NREM) sleep-like electroencephalogram (EEG) features and consolidate sleep after surgery, leading to an increase in stage 2 of NREM sleep, decrease in stage 1 of NREM sleep, prolonged total sleep time, lower nocturnal fragmented sleep, and eventually better subjective sleep quality for patients

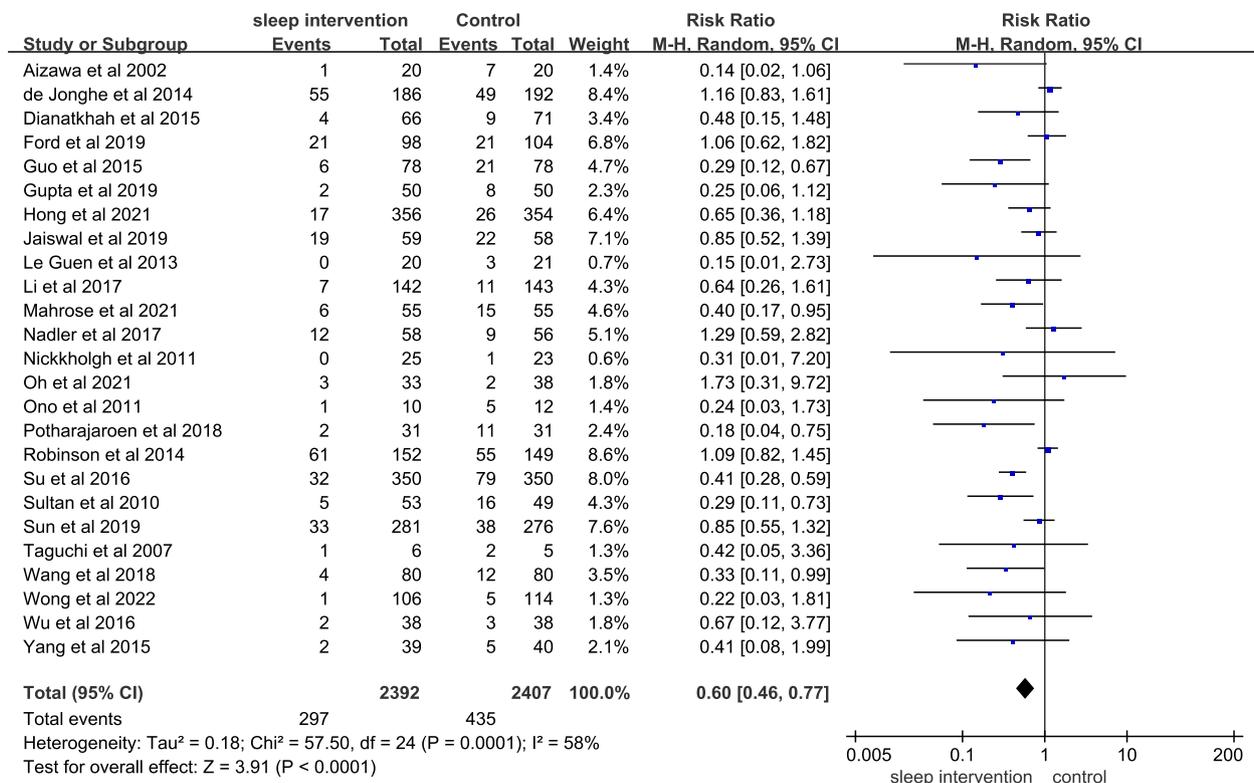


Fig. 3 Forest plots of the pooled incidences of postoperative delirium for the sleep intervention group and the control group. Statistical analyses were conducted using a random-effects model. The size of the squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars = 95% confidence intervals (CIs)

[55]. Our present finding of dexmedetomidine effectively reducing the incidence of POD in patients is consistent with the results of a previous meta-analysis, in which Duan et al. [56] had demonstrated that dexmedetomidine had positive actions on diminishing the risk of POD in adult patients. Notably, we excluded trials in which the patients received dexmedetomidine only during the intraoperative period. The reason for this exclusion was that the objective of this meta-analysis was to investigate the role of sleep interventions on POD incidence, and dexmedetomidine usage only in the intraoperative period was mainly intended for intraprocedural sedation and may not have been associated with sleep interventions. Similarly, we observed that the occurrence of POD was comparatively lower among patients who received bright light therapy, a nonpharmacological method of sleep intervention that helped adjust the circadian rhythm and has a therapeutic effect on sleep disturbances in patients with mental disorders [57, 58]. However, our subgroup analysis revealed that melatonin or melatonin receptor agonists did not significantly affect the incidence of POD. In fact, a study by Wang et al. [59] concluded that the use of melatonin or melatonin receptor agonists during the perioperative

period did not reduce the risk of POD (RR=0.93; 95% CI, 0.70–1.24), which was consistent with our current findings. However, this was not consistent with results from a previous meta-analysis that observed beneficial effects of melatonin and melatonin receptor agonists on perioperative sleep and reduction in the risk of POD (pooled RR=0.49; 95% CI, 0.28–0.88; *p*=0.017) [22]. This inconsistency may be attributed to the heterogeneous design of the included trials (different dosages and timings of melatonin administration, etc.) and the different methods used for assessing the outcome (CAM/CAM-ICU, DSM criteria, etc.). Furthermore, seven trials did not assess the efficacy of intervention on postoperative sleep in patients who received melatonin or melatonin receptor agonists, [21, 37, 42, 44, 46, 48, 49], only one trial reported a statistically positive effect [50], and two trials did not report a significant improvement in sleep between the intervention and control groups [38, 41]. The absence of a formal sleep assessment may have led to an underestimation of the effectiveness of interventions for patients receiving melatonin or melatonin receptor agonists, further adding to the uncertainty of these interventions in reducing the occurrence of POD. Therefore, larger RCTs are required in future

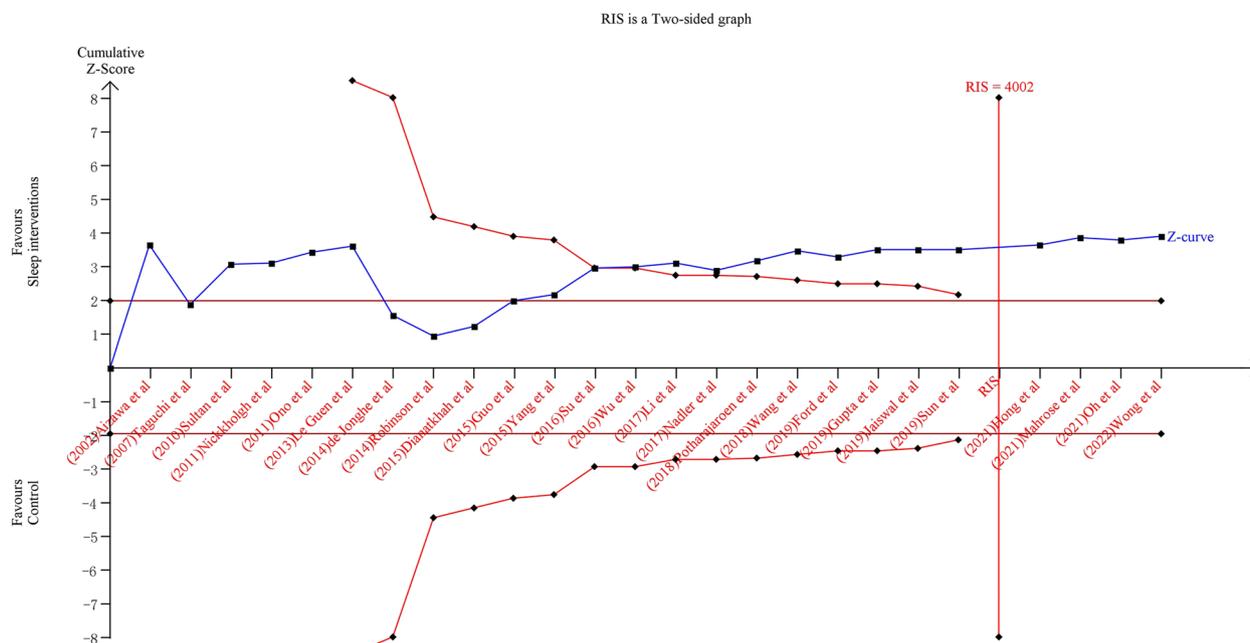


Fig. 4 Trial sequential analysis (TSA) of the sleep interventions for decreasing the incidence of postoperative delirium (POD). A required information size (RIS) of 4002 patients was calculated using the predefined $\alpha=0.05$ (two-sided), $\beta=0.20$ (80% power), an anticipated relative risk reduction of 28.57%, and an event proportion of 21% in the control arm. The blue cumulative Z curve was constructed using a random-effects model. The horizontal brown lines represent the conventional meta-analysis boundary. The horizontal red lines represent the trial sequential monitoring boundary. The cumulative Z curve crosses both conventional meta-analysis boundary and the trial sequential monitoring boundary, and the number of recruited participants is more than the required information size, which represents that the pooled evidence of sleep intervention in decreasing the incidence of POD was sufficient

to investigate whether melatonin or melatonin receptor agonists have a preventive effect on POD.

A substantial body of research has considered obstructive sleep apnea (OSA) as a main risk factor for POD [7, 60–62]. There is a plausible biological link between OSA and POD, as OSA is likely to trigger inflammation, hypoxia, and disrupted sleep patterns, which could contribute to the development of POD [63]. It has been demonstrated that PAP could alleviate these possible triggers and significantly improves the symptoms of OSA [64]. However, the pooled finding in the subgroup analysis of our study did not suggest a protective effect of PAP therapy on decreasing the occurrence of POD in surgical patients who were at risk for OSA. Therefore, sleep interventions targeting OSA (PAP in short-term treatment) may have no role in decreasing postoperative incident delirium. The present meta-analysis only included two trials [34, 43] with a total of 334 participants, and there was significant heterogeneity between the two trials. Thus, due to the limited sample size and significant heterogeneity, the conclusions should be interpreted with caution. Because only one RCT [45] involved the use of earplugs and eye masks, and only one trial [51] included patients

who were administered DFP using diazepam, flunitrazepam, and pethidine to maintain nocturnal sleep rhythm in the perioperative period, we refrained from performing subgroup analysis in both of them. Moreover, our analysis revealed that only the trials that demonstrated effective sleep interventions on postoperative sleep reported a lower incidence of POD. Furthermore, this was true in adult patients undergoing noncardiac surgery, but not in those undergoing cardiac surgery. Additionally, irrespective of the sample size, age, and dosage of dexmedetomidine, sleep interventions appear to be effective in reducing the incidence of POD.

Sleep is a natural state of reduced arousal that plays a crucial role in learning, memory, and cognitive function [65]. It has been reported that sleep disturbances are independent risk factors for POD, which can lead to long-term cognitive dysfunction after surgery [66, 67]. Disruptions in sleep patterns may trigger a process of neuronal apoptosis in regions of the brain that are closely associated with cognitive function [68, 69]. Therefore, neuronal apoptosis is considered one of the pathological factors of sleep disturbance-related cognitive dysfunction. As reported earlier, sleep disturbances are associated with neuroinflammation, alterations in

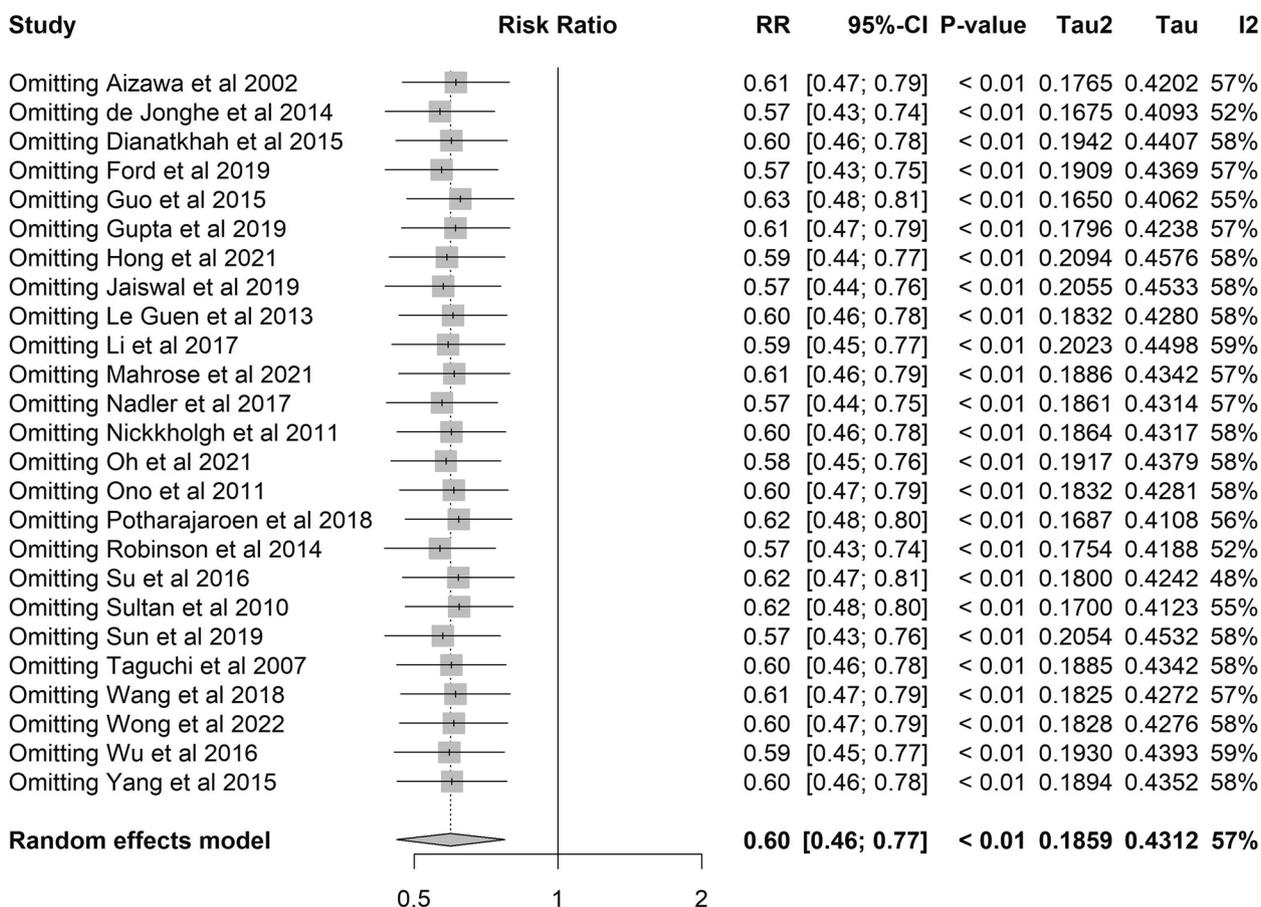


Fig. 5 Sensitivity analysis for sleep intervention in decreasing the incidence of POD. Excluding each trial sequentially and recalculating the pooled risk ratio for the remaining trials was performed using a random-effects model

neurotransmitter activity, and cerebral hypoxic and hypoperfusion injury [68, 70]. Because the possible pathophysiological mechanisms of POD also include neuroinflammation and changes in neurotransmitters [71], sleep disturbances may be associated with POD. Therefore, improving perioperative sleep can be an effective method for attenuating the incidence of POD. Sleep improvement interventions include both pharmacological and nonpharmacological measures. In a meta-analysis, Hu et al. [23] sought and recommended nonpharmacological interventions, such as music therapy, noise reduction, and social support, to enhance sleep in critically ill patients. Compared with a prior meta-analysis of thirteen RCTs, which demonstrated that interventions targeting sleep and circadian health reduced the risk of POD [30], the current meta-analysis included as many trials as possible that used multiple sleep interventions, thus enabling us to analyze the effect of sleep interventions on POD incidence more comprehensively.

The advantages of this meta-analysis are as follows. First, it incorporated a comprehensive collection of trials. Second, both nonpharmacological and pharmacological interventions that are widely used and recommended during the perioperative period were included, resulting in pooled results with high significance. Third, our meta-analysis exhibited no significant publication bias. Further sensitivity analyses also confirmed the consistency and robustness of our findings.

The present study exhibits certain limitations. First, most of the analyses manifested a high degree of heterogeneity, which is an anticipated outcome due to the diverse sleep interventions administered to the participants in the included trials. Second, our meta-analysis did not entail stratification by the type of sleep disturbance. In fact, there are different phenotypes of perioperative sleep disturbances, such as OSA and psychologically based sleep deprivation. These different types of sleep disturbances may have diverse effects on POD, so this could be a potential confounder and may have influenced the current results. Additionally, some

interventions like oral melatonin were administered preoperatively, whereas some interventions like earplugs and masks were administered postoperatively. The focus should also be on the effect of the timing of sleep interventions on POD. Therefore, performing a high-quality meta-analysis with a large sample size is necessary to further determine whether the phenotype of sleep disturbances or the timing of interventions in the perioperative period is related to the incidence of POD. Third, considerable variability in the methods utilized to evaluate both POD and sleep disturbances was observed, which may have also affected the validity and reliability of our pooled results. Fourth, several subgroups analyzed in this meta-analysis exhibited a limited sample size, thereby potentially attenuating the reliability of the synthesized results. Finally, while a significant disparity in the incidence of POD was observed between the group that received sleep interventions and the control group, a substantial proportion of patients did not receive any type of assessment pertaining to perioperative sleep. Moreover, including only articles written in English or Chinese may have affected the internal and external validity of our findings.

5 Conclusions

For adult patients undergoing elective surgery, interventions for improving postoperative sleep were associated with a lower incidence of POD, especially when the intervention effectively improved sleep quality. Considering the heterogeneity of included trials, we should interpret the results with caution. Large-scale RCTs in future are still warranted to confirm the current results.

Abbreviations

AMT	Abbreviated Mental Test
APAP	Auto-titrating positive airway pressure
BLT	Bright light therapy
CABG	Coronary artery bypass graft
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the intensive care unit
CI	Confidence interval
CPAP	Continuous positive airway pressure
DFP	Delirium-free protocol
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
GSQS	Groningen Sleep Quality Score
ICU	Intensive care unit
ICDSC	Intensive Care Delirium Screening Checklist
ISI	Insomnia Severity Index
NEECHAM	Neelon and Champagne Confusion Scale
NREM	Nonrapid eye movement
NRS	Numeric Rating Scale
Nu-DESC	Nursing Delirium Screening Scale
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
POD	Postoperative delirium
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RASS	Richmond Agitation and Sedation Scale
RCSQ	Richards-Campbell Sleep Questionnaire

RCTs	Randomized controlled trials
RIS	Required information size
RR	Relative risk
SICU	Surgical intensive care unit
TSA	Trial sequential analysis
TSMB	Trial sequential monitoring boundary

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s44254-023-00027-1>.

Additional file 1.

Additional file 2. Search strategy.

Additional file 3.

Additional file 4: Supplemental Fig. 1. Forest plot showing pooled analysis of studies categorized into bright light group, dexmedetomidine group, melatonin group, and PAP group. Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI). PAP, positive airway pressure.

Additional file 5: Supplemental Fig. 2. Forest plot showing pooled analysis of studies with different effect of sleep interventions. Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI).

Additional file 6: Supplemental Fig. 3. Forest plot showing pooled analysis of studies with different delirium diagnosis tools. Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI).

Additional file 7: Supplemental Fig. 4. Forest plot showing pooled analysis of studies categorized into non-cardiac surgery, cardiac surgery, or both cardiac and non-cardiac surgery. Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI).

Additional file 8: Supplemental Fig. 5. Forest plot showing pooled analysis of studies categorized into studies with sample size less than 100 and greater than or equal to 100. Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI).

Additional file 9: Supplemental Fig. 6. Forest plot showing pooled analysis of studies categorized into studies with median/mean age less than 65 years old and greater than or equal to 65 years old. Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI).

Additional file 10: Supplemental Fig. 7. Forest plot showing pooled analysis of studies categorized into ICU patients (sedative dose or low-dose of dexmedetomidine) and non-ICU patients (low-dose or mini-dose via PCA of dexmedetomidine). Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI). PCA, patients-controlled analgesia.

Additional file 11: Supplemental Fig. 8. Forest plot with subgroup analysis 'preoperatively', 'postoperatively', 'preoperatively and postoperatively'. Statistical analyses were conducted using the random-effects model. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % confidence intervals (CI). PCA, patients-controlled analgesia.

Additional file 12: Supplemental Fig. 9. A Funnel plot with pseudo 95% confidence interval. Random-effects meta-analysis. B Funnel plot with pseudo 95% confidence interval. Fixed-effects meta-analysis.

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Not applicable.

Authors' contributions

Design of meta-analysis: Hailong Dong, Chong Lei, and Xuemiao Tang. Search strategy: Xuemiao Tang and Jia Li. Screening of results: Xuemiao Tang and Jia Li. Data extraction: Bo Yang and Xuemiao Tang. Risk of bias: Jia Li and Bo Yang. Statistical analysis: Bo Yang and Jia Li. Drafting of manuscript: Xuemiao Tang. Revision of manuscript: Hailong Dong, Chong Lei, and Xuemiao Tang.

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Availability of data and materials

The data and materials generated and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

All authors listed above approved the submission of final manuscript.

Competing interests

The authors declare no conflict of interest.

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