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CLINICAL REVIEW

Promoting sleep and circadian health may prevent postoperative delirium: A systematic review and meta-analysis of randomized clinical trials

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SUMMARY

This systematic review with meta-analysis and trial sequential analysis of randomized clinical trials aimed to clarify the efficacy of sleep and circadian interventions on preventing postoperative delirium. The search and screening identified 13 trials with great heterogeneity in interventions, surgery types as well as methods for evaluating delirium, sleep and circadian rhythms. Meta-analyses revealed that sleep and circadian interventions were associated with decreased incidences of postoperative delirium (pooled relative risk (RR) = 0.48, 95% confidence interval (CI) = 0.29 to 0.78) compared with control. The pooled incidences of delirium for patients receiving interventions and no intervention (control) were 8.6% and 20.7% respectively. Results of the trial sequential analysis supported the interpretation that sleep and circadian interventions significantly diminished delirium compared to control. Subgroup analysis found that interventions that showed positive efficacy on sleep and circadian outcomes ($p < 0.001$), but not those without improvements ($p = 0.114$) or without assessments ($p = 0.858$), were associated with decreased risk of delirium. Dexmedetomidine sedation ($p < 0.001$) and timed bright light exposure ($p = 0.006$) appeared to reduce postoperative delirium. In summary, currently only limited evidence suggests strategies targeted at sleep and circadian health as a useful way to prevent postoperative delirium.

Introduction

Postoperative delirium, which manifests as acute and fluctuating alterations of consciousness, attention, and cognition, affects 11%–51% of patients after major surgery [1,2]. Postoperative delirium independently predicts prolonged intensive care unit (ICU) and hospital stay, increased mortality, and long-term postoperative cognitive dysfunction [3,4] and is an economic burden to healthcare systems [5]. Identifying the modifiable risk factors and implementing the risk reduction strategies has the potential to decrease the incidence of postoperative delirium [6,7].

Sleep and circadian rhythm disruptions are frequently reported after surgery. These disruptions include sleep fragmentation, a decrease in deep non-rapid eye movement (NREM) sleep, an initial reduction and subsequent rebound increase in rapid eye movement (REM) sleep, and daytime sleepiness [8,9]. More than 40% of patients reported sleep problems during the first night after surgery [10]. The sleep problems even continued several days after surgery [11]. Sleep and circadian rhythm disruption likely contributes to the development of postoperative delirium by itself or by interacting with pain and inflammation [10,12–16]. The foregoing findings have encouraged efforts to promote postoperative sleep and circadian health to diminish the incidence of postoperative delirium [17–20].

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Abbreviations

CAM	Confusion Assessment Method
CI	confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
DRS	Delirium Rating Scale
ICD-10	the 10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICDSC	intensive care delirium screening checklist
ICU	intensive care unit
ITT	Intention-to-treat
NEECHAM	Neelon and Champagne
NREM sleep	non-rapid eye movement sleep
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized clinical trial
REM sleep	rapid eye movement sleep
RR	relative risk
SD	standard deviation
SMD	standard mean difference

The purpose of this study was to critically review available randomized clinical trials (RCTs) that assessed sleep promotion and circadian intervention strategies for preventing postoperative delirium, and to determine the pooled efficacy of interventions using the meta-analysis and trial sequential analysis method.

Methods

This systematic review and meta-analysis was conducted following the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (see Table S1) [21].

Search strategy

A systematic search of PubMed, Embase, Cochrane Library and CINAHL databases was performed for articles dealing with the topic of promoting sleep and circadian health to prevent postoperative delirium. The last search was done on April 30, 2019. The search key words used included sleep (including sleep* or night* or circadian or insomnia*); delirium (including delirium, confusion, acute confusional state or acute confusional syndrome) and postoperative (including postoperative, operation, surgery, anaesthesia or anesthesia). For details of the search strategy, see Appendix S1. No language or region restriction was used. Studies recruiting children were excluded. The reference lists of reviews and meta-analyses were confirmed and the related articles of identified studies were further searched using “Google Scholar” to identify potentially eligible studies.

Study selection

The search of databases returned 2894 reports. H. Zhang and Y. Lu performed the screening by reading the title and abstracts using the following predefined criteria. Inclusion criteria were: 1) RCTs which assessed the roles of sleep promotion and circadian intervention in preventing postoperative delirium; 2) all the recruited patients were ≥18 years of age; 3) the assumed main effect of intervention was to promote postoperative sleep and circadian health; and 4) the incidences of postoperative delirium were clearly reported. The following types of studies were excluded: 1) case reports, comments, editorials, guidelines, perspectives, meeting abstracts and erratum; 2) patients with delirium before surgery; 3) homogeneous populations with certain brain diseases or mental disorders (e.g., alcohol withdrawal syndrome, stroke, dementia, schizophrenia, bipolar disorder and depression); 4) non-surgical patients; 5) interventions included sleep promotion and circadian intervention in a comprehensive program and the independent effect of sleep and circadian intervention cannot be derived, and 6) comparators which may increase the risk of delirium such as benzodiazepines and anticholinergic drugs [7]. After screening, H. Zhang and Y. Lu read the full texts of 47 studies to assess their eligibility. Disagreements were resolved by including Y.W. Li (see the PRISMA study flow diagram (Fig. 1) for complete description).

Data extraction

L. Wang and Y.W. Li used a pre-designed data extraction form to extract the data. The information collected included the primary author, publication year, country of origin, study design and the types of surgery. The participant characteristics such as gender, age, number of cases recruited, existing illness and the inclusion and exclusion criteria were also extracted. Additional metrics included intervention strategies (type, dosage, duration and frequency), delirium diagnosis criteria and the incidence, severity and duration of delirium, sleep and circadian evaluation tool and outcomes, and the follow-up. Disagreements were resolved by including X.Y. Shi for further discussion. Dichotomous data were converted into incidences for data syntheses and continuous data were recorded using mean and standard deviation (SD).

Quality assessment of included trials

The methodologic quality was evaluated independently by L. Wang and Y.W. Li with discrepancies resolved by including X.Y. Shi. Both a delirium-specific scoring system from our previous meta-analysis [6] and the Cochrane risk of bias assessment methods were used. The scoring system included nine items with a full score of 13. Specifically, scores of 2 (proper methods with adequate description), 1 (maybe proper but inadequate description), or 0 (improper methods) were given for randomization, allocation concealment, and intervention blinding. If delirium was screened at least one time per day during the first three postoperative days, two points were given. If delirium was screened at least one time per day since the first postoperative day for no more than three d, one point was given. Otherwise, no point was given to a single study. One point was given if withdrawal or dropouts were described clearly; the outcomes were analyzed based on intention to treat (ITT) analysis or postoperative delirium was diagnosed by validated methods. The validated criteria included the Diagnostic and Statistical Manual of Mental Disorders, 1987 (DSM-III), DSM-III-R (1994), DSM-IV (1999), DSM-V (2013), the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, 1992 (ICD-10), or clinical diagnostic tools based on these such as the Confusion Assessment Method (CAM), Delirium Rating Scale (DRS), Neelon and Champagne (NEECHAM) Confusion Scale and ICDSC (intensive care delirium screening checklist) [22]. If grouping was blinded to delirium assessors or delirium risk was similar between groups, one point was given. Otherwise, no point was given. A study with a score of less than nine was arbitrarily considered with low quality. The Cochrane risk of bias assessment table was further used to evaluate the risk of bias on random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting,

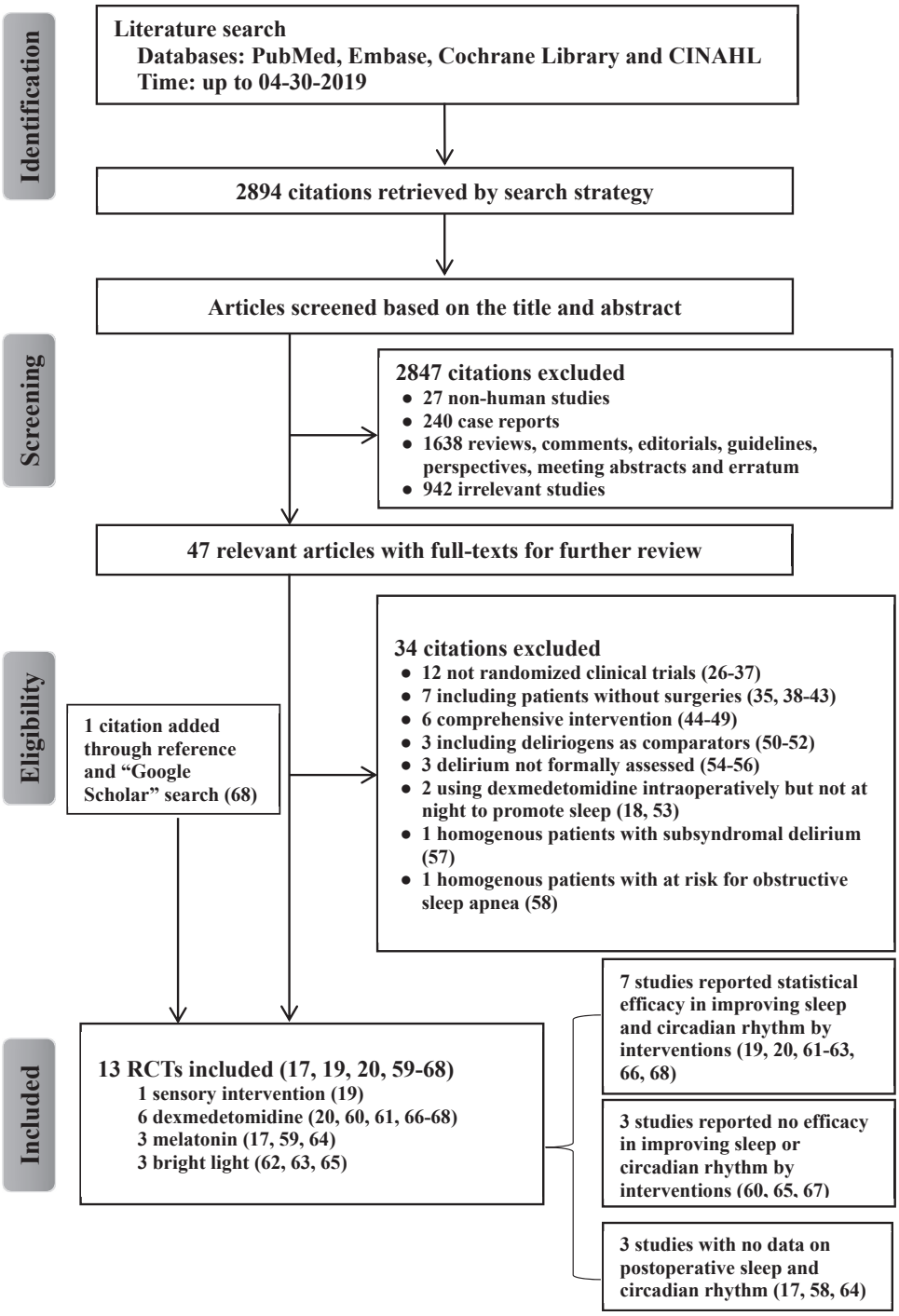


Fig. 1. Flow chart of identification, screening, review and selection of studies based on the PRISMA study flow diagram.

blinding of delirium assessment, solid delirium diagnosis criteria, similar delirium risk and sufficient follow-up for screening delirium based on the standard Cochrane criteria (Fig. 2).

Outcome measures

The primary aim was to determine whether sleep promotion and circadian interventions would decrease the incidence of postoperative delirium. Other outcome measures included the duration and severity of postoperative delirium.

Data analyses

Meta-analyses were performed using STATA 12 software (StataCorp, College Station, TX, USA). Significant heterogeneity was considered present at chi-square ($\chi 2$) $p < 0.10$ or I-square (I^2) > 50% [23]. A fixed effect parametric approach weighted with inverse variance was used for pooled analysis if no heterogeneity was found. Otherwise, a random-effects Mantel-Haenszel model was used. For dichotomous data, the pooled relative risk (RR) and pooled incidences with 95% confidence intervals (CI) was calculated. Sources of heterogeneity were investigated for the following

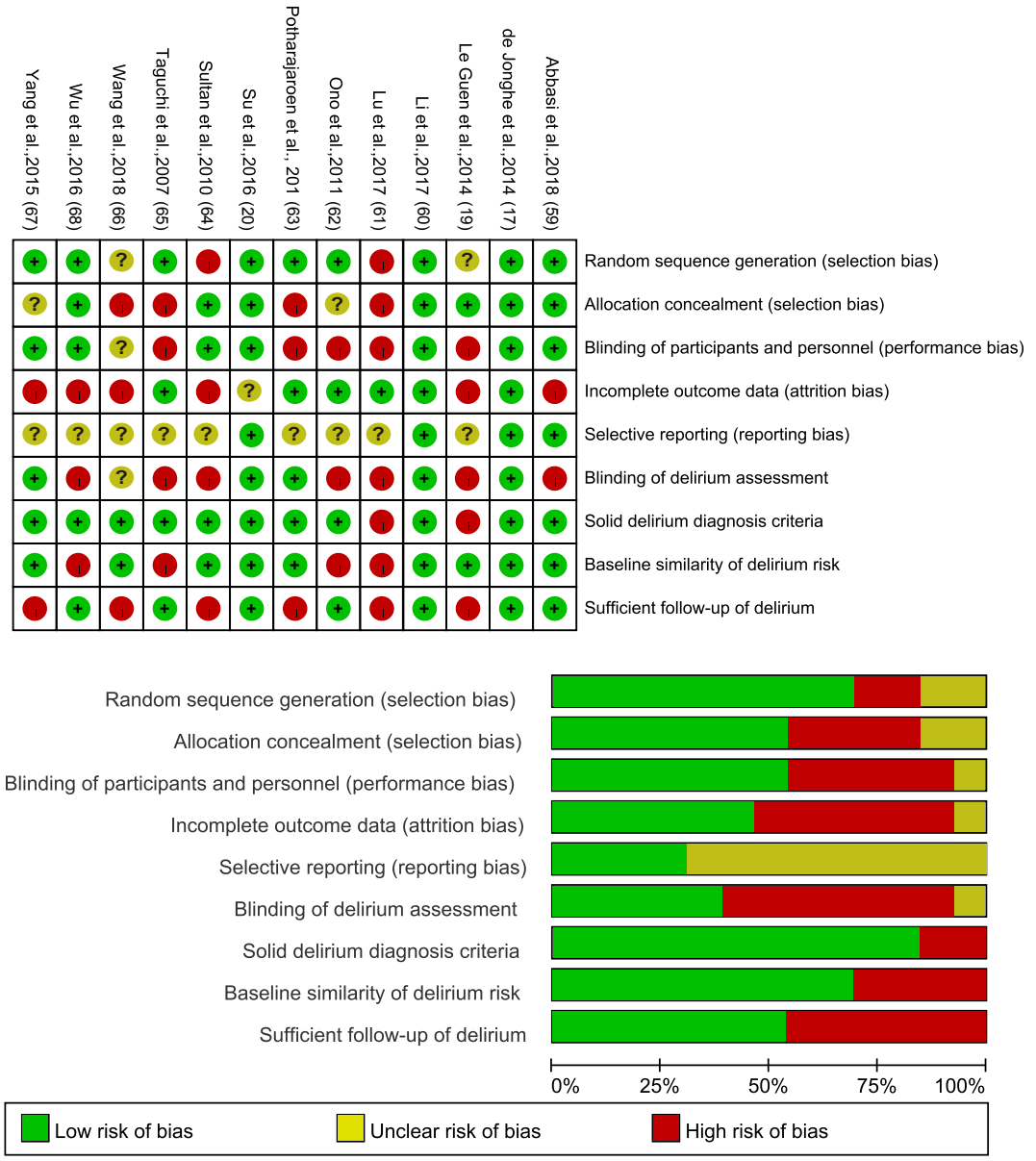


Fig. 2. Cochrane assessment for risk of bias of included studies.

pre-specified factors: efficacy of interventions (positive, negative or not evaluated), surgical diversity (diversified or single type), types of strategies (sleep promotion or circadian intervention), study quality (high or low), sample sizes (>50 patients per arm or not), and reported incidences of delirium (≥20% or <20%) by performing subgroup analysis. Publication bias was assessed by visual inspection of the funnel plot (Fig. 6) and Begg's test. For all the analyses, $p < 0.05$ (two-tailed) was considered statistically significant.

Meta-analysis may increase the risk of type I error [24]. To confirm the pooled results, trial sequential analysis was performed using the TSA 0.9.5.10 beta software (http://www.ctu.dk/tsa) [25]. We calculated the required information size using $\alpha = 0.05$ (two tailed) and $\beta = 0.20$ (power 80%). The pooled incidences of delirium for the intervention and control group were used for the estimated event proportions. The trial sequential monitoring boundaries based on the Lan-DeMets α-spending function that controls the overall type I error by spending it in an appropriate manner are applied. The series of Z statistics after each consecutive trial comprise the cumulative Z-curve. If the cumulative Z-curve crosses both the conventional meta-analysis boundary and the trial sequential monitoring boundary, and the number of patients recruited is greater than the required information size, a sufficient level of evidence is confirmed. Otherwise, the evidence is considered insufficient and indicates that more trials are needed.

Results

Study selection

Fig. 1 illustrates the process of study search, screening, and selection. The search retrieved 2894 records. Preliminary title and abstract screening excluded 2847 citations. After full-text review, 34 publications were excluded due to absence of the following features. Twelve studies did not use a randomized controlled

design [26–37]; seven studies included non-surgical patients [35,38–43]; six studies used a comprehensive delirium prevention bundle including sleep promotion [44–49]; three studies that used deliriogenic medications as comparators including oxazepam [50], propofol [51] and diazepam/flunitrazepam/pethidine [52]; two studies used dexmedetomidine intraoperatively but not at night to promote sleep [18,53]; two studies did not evaluate delirium formally [54–56]; one study recruited patients with subsyndromal delirium only [57] and one study included patients at risk for obstructive sleep apnea only [58]. The remaining 12 studies were considered eligible [17,19,20,59–67]. The additional reference search identified one more study [68]. Thereby, 13 RCTs with a sum of 2015 cases were ultimately included.

Study characteristics

Of the included studies, six trials evaluated postoperative dexmedetomidine sedation at night for delirium prevention [20,60,61,66–68]. One study evaluated sleep environment protection with earplugs and eye masks [19]. Three studies used bright light in the morning [62,63,65] and three tested the role of oral melatonin before bed [17,59,64] (Fig. 1). Considering the main effects of interventions, we collapsed the interventions into two categories: sleep promotion (sensory interventions & dexmedetomidine) and circadian interventions (melatonin & timed bright light).

Table 1 describes the patient characteristics, study designs and main outcomes of included studies. Multicenter design was adopted in three studies [17,20,60]. The number of cases included in each study ranged from 20 [61] to 700 [20]. The mean age of patients ranged from 50 [67] to 84 [17] years old. The types of surgery differed among studies, including cardiac surgery [60], arthroplasty [17,64,66], esophagectomy [62,65], free flap surgery [67] and diversified surgeries [19,20,59,61,63,68]. These types of surgeries were with high risk of postoperative delirium according to the European Society of Anesthesiology guideline [7]. However, the reported incidences of postoperative delirium in the control group differed greatly among studies (0 [59] to 42% [62]).

Postoperative sleep and circadian rhythm patterns were evaluated in 10 studies [17,19,20,59,61–64,66,68] while only one study used polysomnography to objectively assess sleep patterns [68]. One study used Bispectral index [61], and one study used Actiwatch [19] to provide an indirect measure of sleep. Two studies utilized an accelerometer and a memory heart rate recorder to record physical activity and heart rate to estimate circadian rhythm [62,65]. The subjective sleep indexes used included Spiegel scale [19], Numeric Rating Scale (NRS) [20,60,66–68] and the Insomnia Severity Index (ISI) score [63].

Study qualities

The quality score of each item for each included trial is detailed in Table S2. The overall score ranged from 2 [61] to a maximum score of 13 [17,20,60]. Applying a cut-off of nine revealed seven studies of high quality [17,20,59,60,63,67,68] and six low-quality trials [19,61,62,64–66]. The common defects identified in trial assessment included improper allocation concealment (six studies), the lack of blinding of patients and personnel (six studies), the lack of blinding of delirium outcome assessors (eight studies) and insufficient follow-up for delirium screening (seven studies). Fig. 2 shows the detailed risk of bias for each study based on the Cochrane criteria.

Systematic review of outcomes: sleep promotion

We identified seven studies with sleep promotion strategies, either by sensory intervention [19] or by dexmedetomidine [20,60,61,66–68].

Le Guen et al. reported that using earplugs and eye masks during the first postoperative night induced better sleep quality compared with standard care, as evaluated by the Spiegel scale. These devices also decreased the need for a nap but had no effect on sleep length indicated by Actiwatch monitoring [19]. This study reported no differences in the incidences of delirium between sensory interventions and control. It was evaluated as having low research quality.

Six studies evaluated the role of low-dose dexmedetomidine infusion at night in preventing postoperative delirium [20,60,61,66–68]. The infusion rate of dexmedetomidine at night was set at 0.1 ug/kg/hour in four studies [20,60,66,68] and at 0.2 to 0.7 ug/kg/hour in two studies [61,67]. Of these studies, one high-quality study performed polysomnography monitoring of sleep throughout the duration of low-dose dexmedetomidine infusion [68]. This study recruited 38 patients per arm and found that dexmedetomidine infusion increased the percentage of stage N2 sleep, prolonged the total sleep time, decreased the percentage of stage N1 sleep, increased the sleep efficiency, and improved the subjective sleep quality. There was no significant difference in the incidences of delirium between dexmedetomidine and control. Lu et al. used BIS to monitor sleep and found dexmedetomidine could increase sleep time and sleep efficiency but could not prevent delirium [61]. This study was evaluated as having low quality and recruited 20 patients only.

Two studies reported that dexmedetomidine sedation was associated with a concomitant improvement in subjective sleep evaluated by NRS and corresponding reduction in delirium assessed by CAM-ICU [20,66]. Both studies recruited more than 50 patients per arm and were evaluated as having high-research quality.

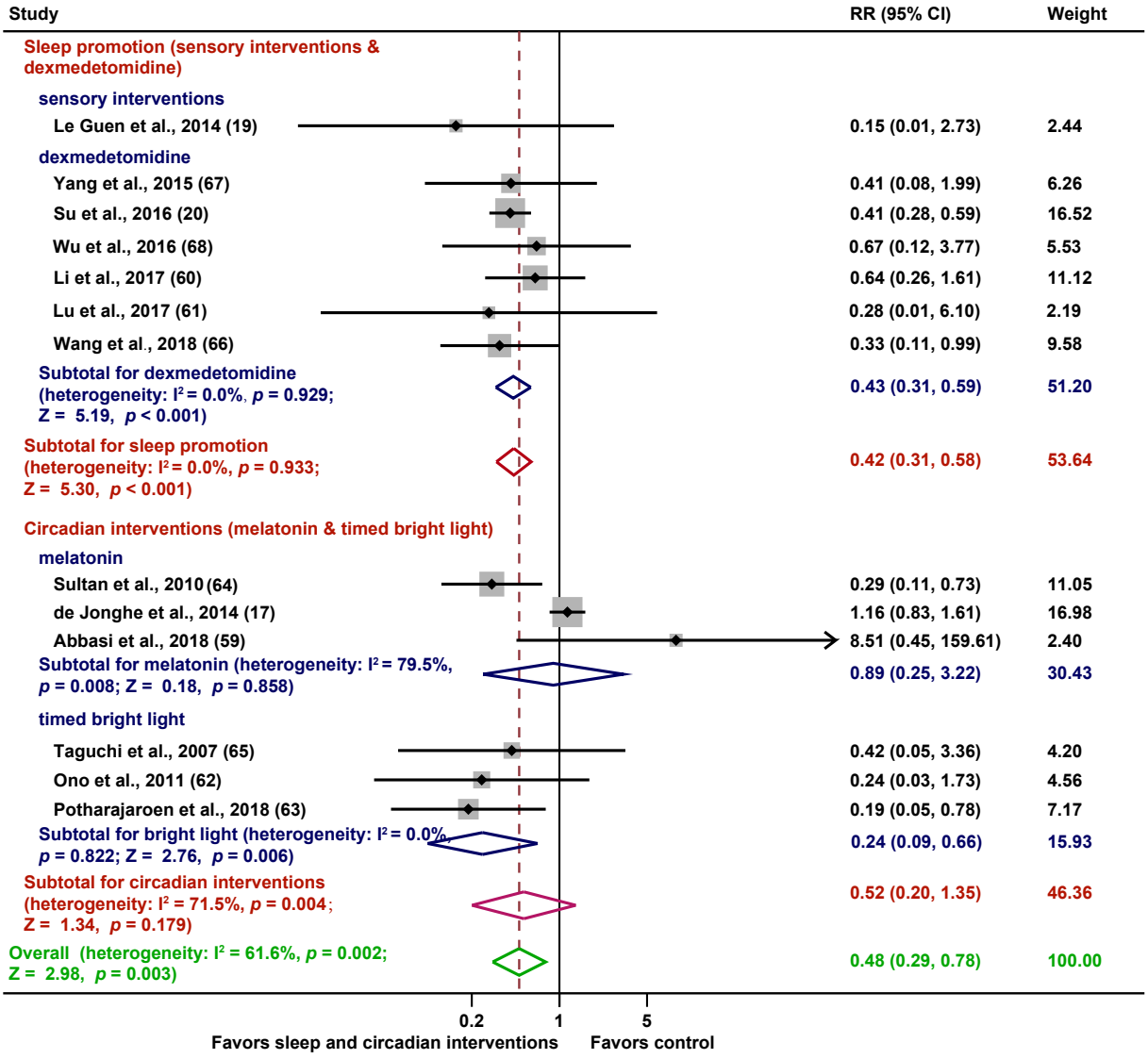
Two high-quality studies also infused low-dose dexmedetomidine in an effort to prevent delirium [60,67]. Both reported no improvements in sleep quality evaluated by NRS and no reductions in the incidences of delirium evaluated by CAM-ICU.

Systematic review of outcomes: circadian interventions

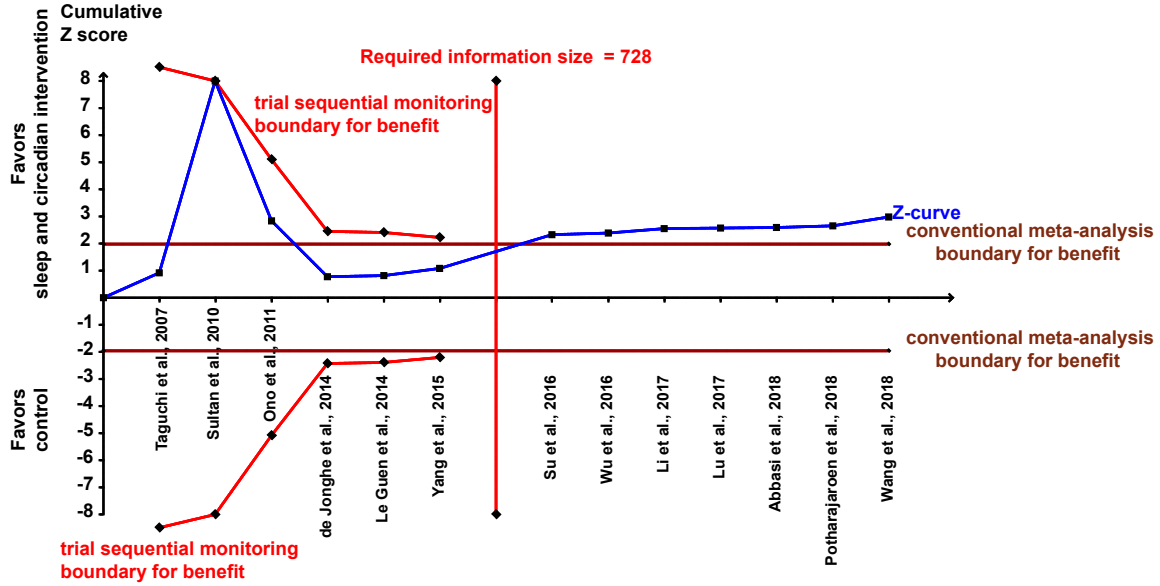
We identified six studies with interventions targeted at circadian rhythm. Three studies tested the delirium-preventive effects of melatonin [17,59,64]. Five mg of melatonin was given at night and before surgery in the study by Sultan et al., during which reduced risk of delirium occurrence by melatonin was observed [64]. In the other two studies, patients were administered 3 mg of melatonin for five consecutive days after surgery, but the studies reported no decrease in the incidences of delirium by melatonin [17,59]. The three studies did not measure postoperative sleep and circadian rhythm changes.

Timed bright light was tried in an effort to prevent delirium in three studies [62,63,65]. Potharajaroen et al. found that bright light at morning lowered ISI scores and reduced the likelihood of delirium evaluated by CAM-ICU compared with control [63]. Ono et al. found bright light could reduce movements at night when evaluated by an accelerometer and a memory heart rate recorder [62]. They also found a trend towards reduced risk of delirium but without significant differences. Taguchi et al. reported that bright light therapy reduced the delirium score, but not the incidences of delirium [65]. Changes in the circadian rhythm of patients were also not detected [65]. Notably, we evaluated both studies [62,65] as having low-quality and recruiting a small number of patients.

A forest plot of meta-analysis



B trial sequential analysis



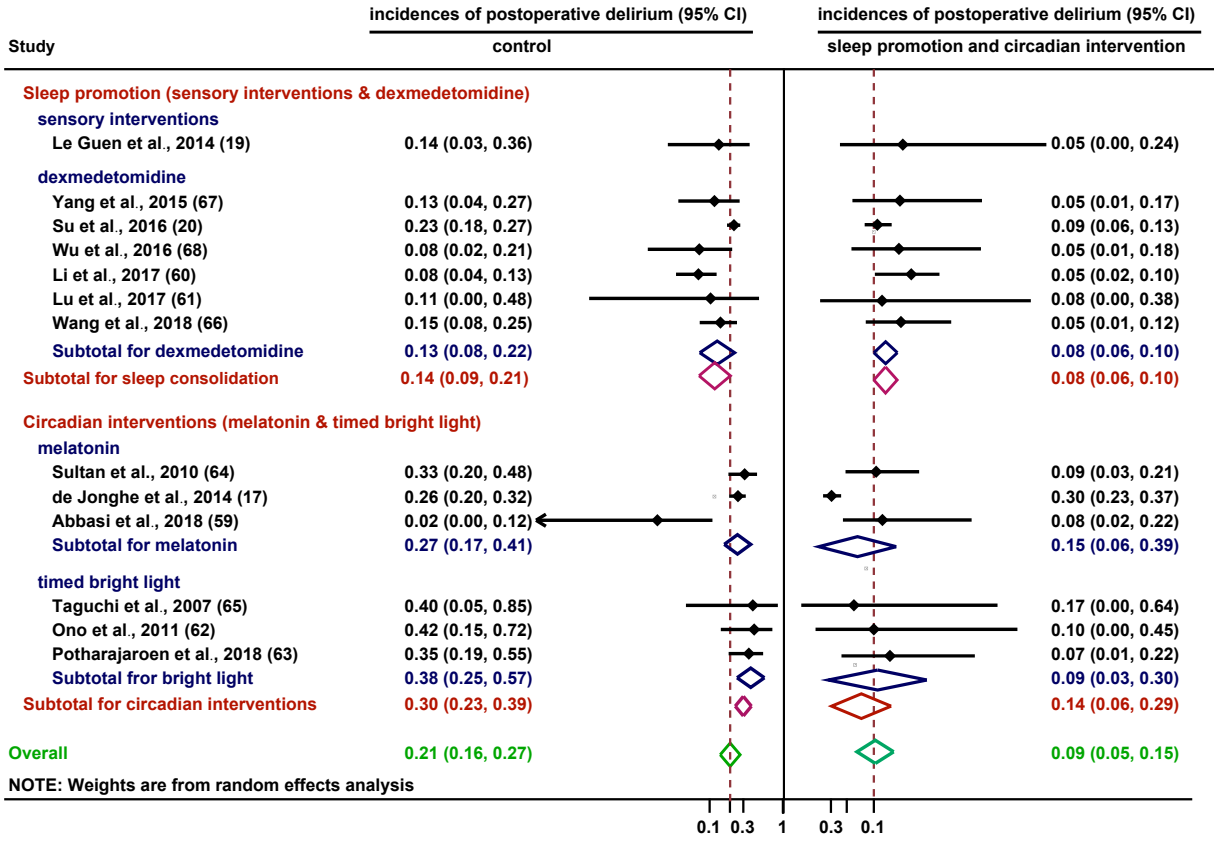


Fig. 4. Forest plot of the pooled incidences of postoperative delirium for control group (left) and the group with sleep promotion and circadian intervention (right). Statistical analyses were performed using the random effects model.

Meta-analysis and trial-sequential analysis results

There was significant heterogeneity among the 13 trials ($p = 0.002$, $I^2 = 61.6\%$). Meta-analysis using the random effects model revealed that strategies targeted at sleep promotion and circadian rhythm resynchronization were associated with lower incidence of postoperative delirium compared with control (pooled RR = 0.48, 95% CI = 0.29 to 0.78, $p = 0.003$, Fig. 3A). The pooled incidences of delirium based on a random effects model were 8.6% (95% CI = 4.9%–15.2%) for patients receiving sleep and circadian interventions and 20.7% (95% CI = 15.7%–27.2%) for control (Fig. 4). This result was further confirmed by trial sequential analysis during which the cumulative Z-curve crossed both the conventional meta-analysis boundary and the trial sequential monitoring boundary for benefit. Moreover, the recruited number of patients exceeded the required information size (Fig. 3B). Sensitivity analysis did not find that any single study could make a significant impact on the pooled relative risks (Fig. 5). No significant publication bias was found by Begg's test ($p = 0.161$) and visual inspection of the funnel plot (Fig. 6).

Subgroup analysis: efficacy of interventions

As regards the efficacy of interventions on sleep and circadian rhythms, we identified seven trials in which interventions had a statistically positive effect versus control [19,20,61–63,66,68]. Three studies reported no significant differences in sleep and circadian rhythm patterns between interventions and control [60,65,67]. Three studies did not evaluate the effect of intervention on postoperative sleep and circadian rhythm [17,59,64]. Subgroup analysis identified that interventions efficacious for promoting sleep and circadian health were efficacious for preventing delirium ($p < 0.001$). By contrast, trials that did not find improvements in postoperative sleep and circadian rhythm among those receiving study intervention similarly did not find a reduction in post-operative delirium among study patients ($p = 0.114$). Likewise, trials that did not assess postoperative sleep and circadian rhythm did not find a reduction in postoperative delirium among those receiving study intervention ($p = 0.858$) (Fig. 7). By performing subgroup analysis, a small inter-trial heterogeneity was observed for interventions that showed positive efficacy on sleep outcomes

Fig. 3. Effects of sleep promotion and circadian intervention versus control on the incidence of postoperative delirium. (A) Summary relative risks (RRs). Values are presented as RR and 95% confidence intervals (CI). Statistical analyses were performed using the random effects model. (B) Trial sequential analysis. The series of Z statistics after each consecutive trial comprise the cumulative Z-curve (blue line). The trial sequential monitoring boundary (red line) was obtained based on the Lan-DeMets α-spending function that controls the overall type I error during meta-analysis. Z-values ±1.96 correspond to the conventional $P = 0.05$ in a two-tailed hypothesis test and were drawn as the conventional meta-analysis boundary (brown). A diversity-adjusted information size of 728 participants was calculated based on the pooled delirium rates of 20.7% in the control group and 8.6% in the sleep intervention group, $\alpha = 5\%$ (two tailed), and $\beta = 20\%$. The cumulative Z-curve crosses both the traditional meta-analysis boundary and the trial sequential monitoring boundary and the number of recruited patients is bigger than the required information size, which means the pooled evidence for sleep promotion and circadian intervention was confirmed. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

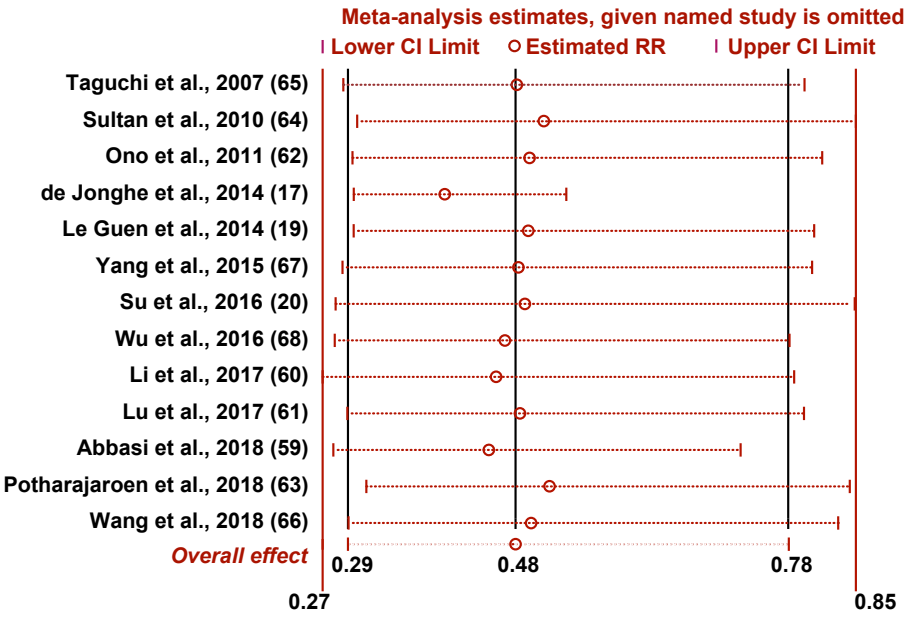


Fig. 5. Sensitivity analysis for sleep promotion and circadian intervention in reducing the incidences of postoperative delirium. Pooled data were expressed as summary relative risks (RRs) and 95% confidence intervals (95% CIs).

($p = 0.904$, $I^2 = 0\%$) and those with no sleep improvements ($p = 0.858$, $I^2 = 0\%$) or but not those without sleep assessments ($p = 0.008$, $I^2 = 79.5\%$).

Subgroup analysis: types of interventions

Subgroup analysis found that interventions targeted at sleep promotion (seven studies with 1361 patients) were associated with reduced incidence of delirium (pooled RR = 0.42, 95% CI = 0.31 to 0.58, P < 0.001, Figs. 3 and 7). This subgroup included six studies using dexmedetomidine [20,60,61,66–68]. Statistics showed a positive role of dexmedetomidine in reducing the incidences of postoperative delirium compared with vehicle (pooled RR = 0.43, 95% CI = 0.31 to 0.59, Figs. 3 and 7). The pooled incidences of postoperative delirium for dexmedetomidine and vehicle were 8% and 13% respectively (Fig. 4).

As regards the circadian rhythm interventions, the synthesized results did not find a reduction in postoperative delirium (pooled RR = 0.52, 95% CI = 0.20 to 1.35, $P = 0.179$, Figs. 3 and 7). We further separated the efficacy of timed bright light (three studies with 94 patients) and melatonin (three studies with 560 patients). The pooled results showed no significantly reduced incidences of postoperative delirium by melatonin administration (pooled RR = 0.89, 95% CI = 0.25 to 3.22, Figs. 3 and 7). The pooled incidences of postoperative delirium for melatonin and control were 15% and 27% respectively (Fig. 4). The pooled RR

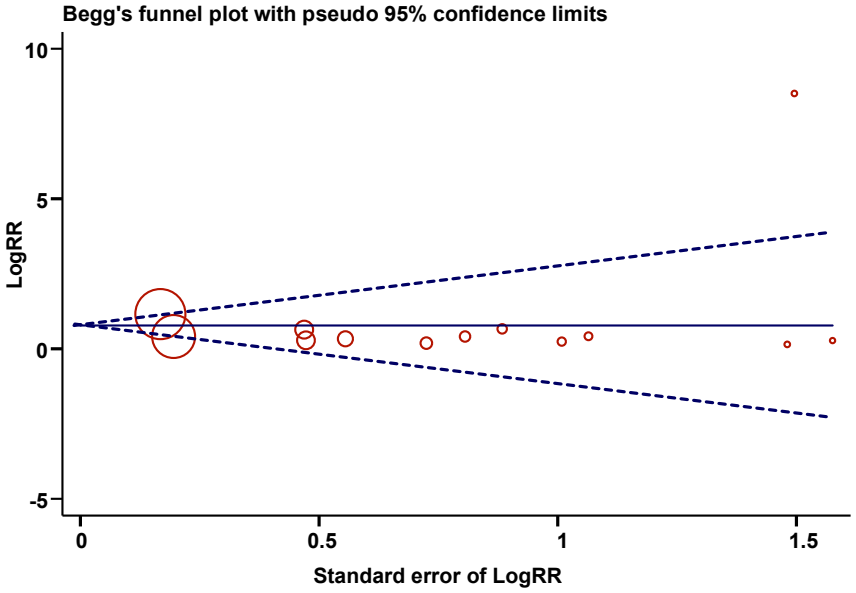


Fig. 6. Funnel plot with LogRR (relative risk) as a function of its standard error for the incidence of delirium. The solid horizontal line represents Log of the pooled relative risk. The upper and lower dashed lines illustrate the 95% confidence interval of LogRR. Each circle represents a single study. The diameter of the circle indicates the number of cases included.

Table 1
Characteristics of included studies evaluating the efficacy of sleep and circadian interventions to prevent postoperative delirium.

Study	Types of interventions	Strategy	Age (y)	Surgery type	Study Quality	delirium screening	Incidence (n/total) (%); *P* value	Delirium Duration or Severity	Sleep promotion results
Le Guen et al., 2014 [19]	sleep promotion (sensory interventions & dexmedetomidine)	earplugs and eye masks for the first postoperative night	I1: 62 ± 3 con: 59 ± 3	major non-cardiac surgery	low	Not specified; POD 1	I1: 0/20 (0) con: 3/21 (14.3%); $P = 0.232$	Not evaluated	Protective devices were associated with better sleep quality by the Spiegel scale ($P = 0.006$), less need for nap ($P < 0.001$), but had no effect on sleep length indicated by Actiwatch.
Yang et al., 2015 [67]	sleep promotion (sensory interventions & dexmedetomidine)	dexmedetomidine (0.5 ug/kg before the completion surgery and 0.2 to 0.7 ug/kg/hour until 6:00 am the next morning)	I1: 50 ± 15 con: 51 ± 12	free flap surgery	high	CAM-ICU; POD 1-5	I1: 2/39 (5.1%) con: 5/40 (12.5%); $P = 0.432$	Not evaluated	No improvement in subjective sleep score evaluated by NRS.
Su et al., 2016 [20] Multicenter	sleep promotion (sensory interventions & dexmedetomidine)	dexmedetomidine (0.1 ug/kg/h on the day of surgery until 08:00 h on POD 1)	I1: 74 ± 7 con: 74 ± 7	non-cardiac surgery	high	CAM-ICU; POD 1-7	I1: 32/350 (9.1%) con: 79/350 (22.6%); $P < 0.001$	Not evaluated	Improvement in subjective sleep quality evaluated by NRS ($P < 0.001$).
Wu et al., 2016 [68]	sleep promotion (sensory interventions & dexmedetomidine)	dexmedetomidine (0.1 ug/kg/h for 15 h after surgery)	I1: 74 ± 5 con: 76 ± 6	non-cardiac surgery	high	CAM; POD 1-7	I1: 2/38 (5.3%) con: 3/38 (7.9%); $P = 1$	Not evaluated	Increases in the percentage of stage N2 sleep ($P = 0.048$), sleep efficiency ($P = 0.033$), and subjective sleep quality assessed by NRS ($P = 0.004$).
Li et al., 2017 [60] Multicenter	sleep promotion (sensory interventions & dexmedetomidine)	dexmedetomidine (0.6 ug/kg within 10 min followed by 0.4 ug/kg/hour during surgery, then 0.1 ug/kg/hour until the end of mechanical ventilation	I1: 68 ± 5 con: 67 ± 5	cardiac surgery	high	CAM, CAM-ICU; POD 1-5	I1: 7/142 (4.9%) con: 11/143 (7.7%); $P = 0.341$	Not evaluated	No improvement in subjective sleep score evaluated by NRS.
Lu et al., 2017 [61]	sleep promotion (sensory interventions & dexmedetomidine)	dexmedetomidine (0.2 −0.7 ug/kg/hour for the first postoperative night, 20:00−08:00)	I1: 57 ± 16 con: 59 ± 18	major abdominal surgery	low	Not specified	I1: 0/11 con: 1/9 (11.1%); $P = 0.450$	Not evaluated	Increased sleep time and sleep efficiency indicated by BIS < 85.
Wang et al., 2018 [66]	sleep promotion (sensory interventions & dexmedetomidine)	dexmedetomidine (0.1 ug/kg/h for 48 h after surgery) vs. placebo	I1: 68 ± 6 con: 66 ± 6	knee arthroplasty	low	CAM-ICU; POD 1-3	I1: 4/80 (5%) con: 12/80 (15%) P = 0.035	Not evaluated	Improvement in subjective sleep quality evaluated by NRS on POD 1 and 2 ($P < 0.05$).
Sultan et al., 2010 [64]	circadian interventions (melatonin & timed bright light)	5 mg melatonin at night and 5 mg before surgery	I1: 70 ± 7 con: 72 ± 6	hip surgery	low	AMT, POD 1-3	I1: 5/53 (9.4%) con: 16/49 (32.7%); $P = 0.001$	Not evaluated	Not evaluated
de Jonghe et al., 2014 [17] Multicenter	circadian interventions (melatonin & timed bright light)	melatonin 3 mg in the evening for five consecutive days after admission.	I1: 84 ± 8 con: 84 ± 8	hip surgery	high	DSM-IV, DOSS, POD 1-7	I1: 55/186 (29.6%) con: 49/192 (25.5%); $P = 0.378$	Duration ($P = 0.5$): 2 ± 1.5 *vs.* 22 ± 1.5 day; % of > 2-day delirium ($P = 0.02$): 25.5% *vs.* 46.9% % of > severe delirium ($P = 0.4$): 45.4% *vs.* 53.1%	Not evaluated
Abbasi et al., 2018 [59]	(melatonin & timed bright light)	melatonin 3 mg before sleep for five consecutive days after surgery	Not specified	Not specified	high	CAM-ICU; POD 1-8	I1: 3/36 (8.3%) con: 0/44; $P = 0.087$	Not specified	Not evaluated

(*continued on next page*)

Table 1 (*continued*)

Study	Types of interventions	Strategy	Age (y)	Surgery type	Study Quality	delirium screening	Incidence (n/total) (%); *P* value	Delirium Duration or Severity	Sleep promotion results
Taguchi et al., 2007 [65]	(melatonin & timed bright light)	2-h bright light (5000 lux; 07:30–09:30 am, POD 2–5)	I1: 56 ± 14 con: 59 ± 14	esophageal cancer surgery	low	NEECHAM, POD 1-5	I1: 1/6 (16.7%) con: 2/5 (40%); $P = 0.545$	Severity based on NEECHAM ($P = 0.014$): I1: 6.7 ± 0.7 I2: 21.1 ± 7	No changes in the circadian rhythm of sleep evaluated by an accelerometer and a memory heart rate recorder.
Ono et al., 2011 [62]	(melatonin & timed bright light)	2-h bright light (2500 lux for 15 min; 4000 lux for 1 h; 5000 lux for 15 min; 4000 lux for 15 min; 2500 lux for 15 min in the morning) for POD 2-5	I1: 63 ± 10 con: 64 ± 8	esophageal cancer surgery	low	NEECHAM, DSM-IV; POD 1-6	I1: 1/10 (10%) con: 5/12 (41.7%); $P = 0.162$	Not evaluated	Reduced movements at night on POD 4 and 5 evaluated by an accelerometer and a memory heart rate recorder.
Potharajaroen et al., 2018 [63]	(melatonin & timed bright light)	2-h 5000 lux bright light in the morning, POD 1-3	I1: 68 ± 10 con: 68 ± 13	major surgery	high	DSM-V, CAM-ICU; POD 1-3	I1: 2/30 (6.7%) con: 11/31 (35.5%); $P = 0.006$	Not evaluated	Lowered ISI scores by bright light intervention

Note: AMT, Abbreviated Mental Test; BIS, bispectral index; CAM, Confusion Assessment Method; DOSS, Delirium Observation Screening Scale; DSM, Diagnostic and Statistical Manual of Mental disorders; ICU, intensive care unit; ISI, Insomnia Severity Index; NEECHAM, Neelon and Champagne; NRS, Numeric Rating Scale; POD, postoperative day.

was 0.24 for bright light versus control (95% CI = 0.09 to 0.66, Figs. 3 and 7). The pooled incidences of postoperative delirium for bright light group and control group were 14% and 30% respectively (Fig. 4).

Subgroup analysis: surgical diversity, study quality, the reported incidences of delirium and the number of patients included.

There was a significant decrease in the incidences of delirium by sleep promotion and circadian interventions irrespective of the surgical diversity (diversified or single type), the study quality (high or low), the reported incidences of delirium (≥20% or not), or the number of patients included per arm (>50% or not) (Fig. 7).

Secondary outcome measures: the duration and severity of postoperative delirium

Two studies reported the duration or severity of delirium results. In a small-sized low-quality study by Taguchi et al., bright light exposure was found to diminish the severity of postoperative delirium evaluated using the NEECHAM scale although the incidence of delirium was not lowered [65]. De Jonghe et al. reported that 3 mg of melatonin for five consecutive d failed to reduce the incidence, duration, the proportion of patients with more than two d of delirium or the proportion of patients with severe delirium [17].

Discussion

This study dealt with the topic of whether interventions targeted at sleep and circadian health could decrease the incidence of postoperative delirium. We chose this topic given that sleep and circadian disturbances were associated with postoperative delirium in observational studies [15,16]. We identified 13 trials with great heterogeneity in the types of interventions and their efficacies on sleep and circadian rhythms, surgery types, reported incidences of delirium, study sample sizes, and research qualities. Considering these biases, we initially performed a scoping summary followed by a quantitative review with subgroup analyses. The synthesized data (Fig. 3) supported the interpretation that promoting sleep and circadian health might help to prevent postoperative delirium. The risk of postoperative delirium in patients with sleep and circadian interventions was diminished by about 50% compared with the risk among control patients (Figs. 3A and 4). The meta-analysis results were confirmed by trials sequential analysis as the cumulative Z-score line crossed the trial sequential monitoring boundary for benefit and the number of recruited patients outweighed the required information size (Fig. 3B). Further sensitivity analysis confirmed the consistency of the findings (Fig. 4). Moreover, only data collapsed from interventions that showed statistical efficacy at improving sleep and circadian rhythm were associated with decreased incidences of delirium (Fig. 7). Taken together, the results provide weak evidence that surgical patients receiving sleep promotion and circadian intervention might have reduced risk of postoperative delirium.

Both sleep consolidation and circadian timing of sleep were disrupted in postoperative patients [8,13]. Evans et al. prospectively collected postoperative EEG data and found that loss of sleep on the first postoperative night was an early predictor of subsequent delirium [69]. A before-after study also found that reducing light, sound, and sleep disturbances in an intensive care unit significantly reduced delirium and improved sleep efficiency in medical and surgical intensive care patients [32]. Similarly, our subgroup analysis found that strategies targeted at sleep promotion might help prevent postoperative delirium (Figs. 3 and 7). Specifically, the contribution mainly came from dexmedetomidine infusion at night. Dexmedetomidine was infused at a rate of 0.1–0.7 ug/kg/

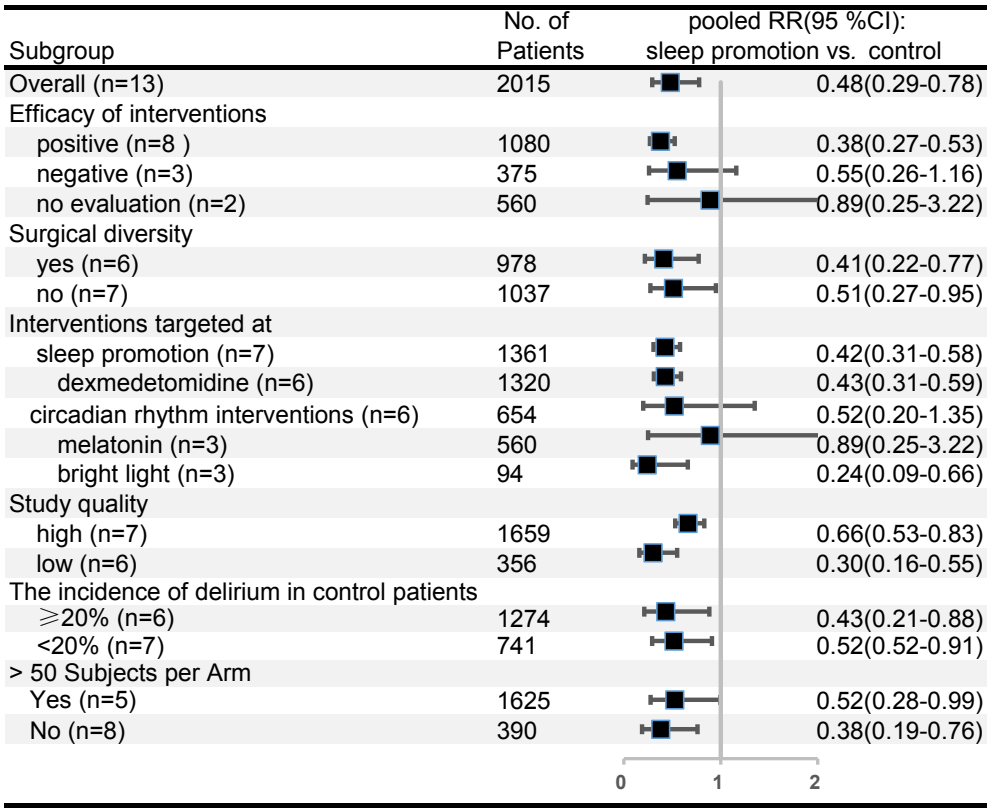


Fig. 7. Subgroup analysis results for sleep promotion and circadian intervention in reducing the incidences of postoperative delirium. Data were expressed as summary relative risks (RRs) and 95% confidence intervals (95% CIs).

hour in the identified six trials [20,60,61,66–68]. About 50% of decrease in the incidences of postoperative delirium by dexmedetomidine was found from the pooled analysis (Figs. 3, 4 and 7). Similarly, Skrobik et al. tested the role of dexmedetomidine infusion at night in preventing ICU delirium [43]. Dexmedetomidine was infused at 0.2 to 0.7 ug/kg/hour to achieve light sedation for patients admitted to the medical-surgical ICU in this well-designed, double-blind trial. The results revealed that nocturnal administration of low-dose dexmedetomidine in critically ill adults reduces the incidence of ICU delirium during the ICU stay (40% versus 27% for placebo versus dexmedetomidine). Different from other sedatives, dexmedetomidine can induce NREM sleep-like EEG characteristics [70] and consolidate sleep in postsurgical or critically ill patients with lower night-time sleep fragmentation index, reduced stage 1 sleep and increased stage 2 sleep [68,71]. Increased EEG delta power (1–4 Hz) is a useful predictor for postoperative delirium [42] and dexmedetomidine sedation did not increase delta power in children [72]. Taken together, these findings support the interpretation that in some patients, dexmedetomidine may diminish postoperative delirium. However, whether the delirium sparing effect is unique to sedation induced by dexmedetomidine remains to be elucidated. Shehabi et al. found sedation depth is inversely related to ICU delirium occurrence [73]. Recent Pain, Agitation/Sedation, Delirium, Immobility and Sleep guidelines make a recommendation of light sedation, regardless of the sedatives chosen [74].

A cohort study found that altered circadian timing of sleep is one key feature of delirium irrespective of cognitive function status [75]. A previous meta-analysis of fifty-three studies found that light therapy was effective in the treatment of circadian disorders of sleep and insomnia reported in postsurgical patients [76]. Our subgroup analysis further found bright light helped reduce the incidence of delirium (Figs. 3A and 7). Of note, the light intensity might matter. Simons et al. used a weaker light intensity and therapy regimen (bluish-white light up to 1700 lux between 09:00 h and 16:00, except for 11:30–13:30 vs. 2500–5000 lux for 2 h) than the intensity used in the included studies (2500–5000 lux, Table 1) and did not find a protective role of light therapy in reducing the incidence and duration of delirium for intensive-care patients [42]. Bright light is thought to act by suppressing the release of endogenous melatonin to help to resynchronize circadian rhythms [77]. However, current meta-analysis of three studies using melatonin did not find a delirium-preventing effect (Fig. 7). This is contraindicatory to conclusions from a recent meta-analysis [78], in which melatonin and melatonin receptor agonists were found to improve sleep and decrease the prevalence of delirium in ICU patients. Only three studies with 560 cases were included and there were very large inter-trial heterogeneities in the current meta-analysis. This adds uncertainty to the conclusion. Further large-scaled RCTs are still needed to evaluate whether melatonin prevents delirium.

Limitations

Caution regarding the use of meta-analysis has long-been appreciated [79]. The present study acknowledges at least three

limitations. Firstly, the diagnostic criteria and the time and frequency of follow-up varied greatly among studies of postoperative delirium. These shortcomings likely impacted the overall effects size (Fig. S1). Secondly, we included studies with strategies targeted at sleep and circadian health, no matter whether sleep and circadian rhythm were evaluated or what metrics were used for evaluation. The use of unreliable subjective sleep scales to measure sleep quality without sleep structure analysis diminish assessment of effective interventions [80]. Moreover, circadian rhythms were evaluated in only two trials [62,65]. Last but not the least, the current study could not determine whether there is a dose–response relationship between the degree of sleep and circadian improvements postoperatively and either the incidence or severity of postoperative delirium.

Future directions

The present results encourage future studies designed to address the limitations noted above and to confirm or refute the effects of specific sleep and circadian intervention on postoperative delirium. Objective measures of sleep during sleep intervention are strongly recommended to ascertain the efficacy of intervention. Previous studies have suggested specific EEG characteristics that may help predict delirium [69,75]. Thus, the use of polysomnography, the gold standard for assessing sleep, will likely provide novel and needed insights into the relationship between sleep and postoperative delirium. Additionally, the assessment of postoperative delirium should use previously validated tools and follow-up over longer time frames. The present results also indicate a need for outcome measures that are better able to determine whether improving sleep and circadian health can simultaneously prevent and treat postoperative delirium.

Conclusion

The current systematic review and meta-analysis found a positive role of sleep promotion and circadian intervention in decreasing the incidences of postoperative delirium. Specifically, low-dose dexmedetomidine at night and timed bright light exposure showed efficacy in preventing delirium. Additionally, our meta-analyses identified complexity and lack of clarity resulting from varied methodological designs and qualities of identified trials. Future clinical trials with more careful assessment of postoperative delirium, objective evaluation of sleep and circadian rhythm, and better control of confounding factors are needed to confirm the efficacy of sleep promotion and circadian intervention as a countermeasure for postoperative delirium.

Practice points

- Sleep promotion and circadian intervention in postsurgical patients may be efficacious in reducing the incidences of postoperative delirium in some patients.
- Low-dose dexmedetomidine induced light sedation at night may diminish postoperative delirium.
- Postoperative timed bright light exposure may be helpful for preventing delirium.

Research agenda

- Objective polysomnography should be used in studies aiming to evaluate the efficacy of sleep promotion in diminishing postoperative delirium.
- Assessment of postoperative delirium should use validated psychometric tests.
- Variables identified as relevant by the present study should be incorporated in the experimental design of future studies on how sleep and circadian interventions alter postoperative delirium.

Authors' contributions

Shi X.Y., Lu Y., and Zhang H. proposed the topic of the meta-analysis. Lu Y., Li Y.W. and Zhang H. performed the literature search and study selection. Wang L., Li Y.W. and Shi X.Y. extracted data and assessed study quality. Lu Y., and Zhang H. performed the data analysis. Lydic R., Baghdoyan H.A. and Zhang H. checked the data, made figures and tables, and prepared and revised the manuscript.

Declaration of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.08.001.

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