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A SYSTEMATIC REVIEW AND META-ANALYSIS EXAMINING THE IMPACT OF SLEEP DISTURBANCE ON POST-OPERATIVE DELIRIUM

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Abstract

OBJECTIVES: Basic science and clinical studies suggest that sleep disturbance may be a modifiable risk factor for post-operative delirium (POD). We aimed to assess the association between pre-operative sleep disturbance and POD.

DATA SOURCES: We searched PubMed, Embase, CINAHL, Web of Science, and Cochrane from inception until May 31st, 2017.

STUDY SELECTION: We performed a systematic search of the literature for all studies that reported on sleep disruption and POD excluding cross-sectional studies, case reports and studies not reported in English language.

DATA EXTRACTION: Two authors independently performed study selection and data extraction. We calculated pooled effects estimates with a random-effects model constructed in Stata® and evaluated the risk of bias by formal testing (Stata® Corp V.14, Texas, USA),

DATA SYNTHESIS: We included 12 studies, from 1,238 citations that met our inclusion criteria. The pooled odds ratio for the association between sleep disturbance and POD was 5.24 (95% CI: 3.61 to 7.60, p <0.001; I^2=0.0%, p=0.76). The pooled risk ratio for the association between sleep disturbance and POD in prospective studies (n = 6) was 2.90 (95% CI: 2.28 to 3.69, p <0.001; I^2=0.0%, p=0.89). The odds ratio associated with obstructive sleep apnea and unspecified types of sleep disorder were 4.75 (95% CI: 2.65 to 8.54, p <0.001; I^2=0.0%, p=0.85), and 5.60 (95% CI:

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3.46 to 9.07, p <0.001; I^2=0.0%, p=0.41), respectively. We performed Begg's and Egger tests for publication bias and confirmed a null result for publication bias (P = .371 and .103, respectively).

CONCLUSIONS: Pre-existing sleep disturbances are likely associated with POD. Whether system-level initiatives targeting patients with pre-operative sleep disturbance may help reduce the prevalence, morbidity and healthcare costs associated with POD remains to be determined.

Keywords

Postoperative; delirium; sleep disturbance; metaanalysis; systematic review; anesthesia

INTRODUCTION

Post-operative delirium (POD), commonly encountered after surgery,[1] is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder.[1, 2] POD remains a leading cause of morbidity in hospitalized patients. [3] Recent studies suggest that clinical care protocols directed at elderly post-surgical patients result in a reduced incidence of POD. [4] Thus, principled strategies to pre-emptively identify and target patients at risk for POD may result in significantly improved peri-operative outcomes.

Sleep is a naturally occurring state of decreased arousal that is crucial for normal immune and cognitive function.[5] Sleep disturbance is associated with increased levels of pro-inflammatory cytokines.[6, 7, 8] Because diagnoses with a high incidence of delirium are also characterized by increased levels of pro-inflammatory cytokines (systemic inflammation), [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] systemic inflammation may be involved in the pathophysiology of delirium, and sleep disturbance may constitute a modifiable risk factor for POD.[24] Therefore, our objective was to determine the association between pre-existing sleep disturbance and POD

MATERIALS AND METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered with the international prospective register of systematic reviews (PROSPERO) (CRD42017070607).

Search strategy

A library sciences specialist designed and implemented a comprehensive literature search of five databases: PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane and Web of Science from inception until May 31, 2017 using the following key word terms: ("Confusion"[25] OR delirium[tiab] OR delirious[tiab] OR confusion*[tiab] OR metabolic encephalopathy[tiab] OR toxic encephalopathy[tiab] OR acute brain dysfunction[tiab] OR acute organic psychosyndrome*[tiab] OR acute psychoorganic[tiab] OR acute psycho organic[tiab] OR clouded[tiab] OR clouding[tiab] OR exogenous psycho*[tiab] OR toxic psycho*[tiab]) AND ("Sleep"[25] OR "Sleep Wake Disorders"[25] OR sleep*[tiab] OR restless leg*[tiab] OR dyssomn* OR parasomn*[tiab] OR

narcolep* OR somnolen*[tiab] OR hypersomn*[tiab] OR insomnolen*[tiab] OR hyposomn*[tiab] OR myoclonus syndrome[tiab] OR hypnogenic paroxysmal[tiab] OR somnamb*[tiab]) AND ("Anesthesia"[25] OR "Anesthetics"[25] OR "Anesthetics" [Pharmacological Action] OR "Surgical Procedures, Operative"[25] OR "Postoperative Care"[25] OR "Postoperative Complications"[Mesh:noexp] OR "surgery"[subheading] OR surgical[tiab] OR surgery[tiab] OR postsurg*[tiab] OR operative[tiab] OR postoperative[tiab] OR anesthes*[tiab] OR anaesthes*[tiab] OR anesthet*[tiab] OR anaesthet*[tiab]). Supplemental Table 1.

Study Selection

Two reviewers (ABF, RI) assessed the retrieved studies independently, including titles, abstracts, and citations to determine whether each citation met inclusion criteria. The full texts of the citations classified as include or unclear were reviewed independently with reference to the pre-determined inclusion and exclusion criteria. Consensus was achieved through discussions with a third reviewer (OA) in cases of disagreement. All citations associated with selected studies were screened for articles that met our inclusion criteria but were not captured by our literature search.

Eligibility was determined if studies were: in adult human population greater than 18 years of age, quantitative with calculated effect measures, randomized controlled trials (RCTs) or prospective or retrospective cohort or case-control studies, electronically accessible, done within 30 days postoperative delirium period. We excluded cross-sectional studies, case reports and studies not reported in English language.

Data Extraction

Two reviewers (ABF, RI) independently extracted data from eligible studies using predesigned forms. Disagreements between the two reviewers were resolved after discussions with a third reviewer (OA). The following data were collected: 1) Name of first author; 2) year of publication; 3) country; 4) study design; 5) study population; 6) mean/median age and age range; 7) type of sleep disorder assessed; 8) period of sleep disorder assessment; 9) sleep quality assessment tool; 10) delirium assessment tool; 11) type of surgery; 12) numerical data on the number of participants in each arm, names of comparators, number of events in each arm, and reported Odds ratios (ORs) and Risk Ratios (RRs); and, 13) variables used for data adjustment or matching. Where multiple effect estimates were reported, we extracted both the crude and adjusted effect estimates reflecting the greatest degree of control for potential confounders.

Quality of Individual Studies and Publication bias.

The quality of included studies was independently assessed by two authors (ABF and RI) using the Newcastle-Ottawa form.[26] The Newcastle-Ottawa form is a standardized and published tool for assessing non-randomized studies. High quality studies were defined as scores of seven or higher, moderate quality as scores of five to six and low quality as less than five. [26] Publication bias was assessed by visual inspection of a funnel plot and formal testing with the Egger's test and Begg's test.[27, 28, 29]

Data Analysis

Analyses were performed using Stata® software (Stata® Corp V.14, Texas, USA). All tests were two-sided, and we considered a *p* value less than 0.05 statistically significant. The crude OR and 95% Confidence Interval (CI) of each study was estimated using number of events on each arm where available, or standard error when the CI was not reported. Heterogeneity among studies was quantified using visual inspection of forest plot, the Cochran's Q statistic ($p<0.05$) and I^2 statistic. We used the conservative random effects model of DerSimonian and Laird[30] to pool all ORs. Heterogeneity was explored in subgroup analysis of: 1) study size; 2) study design; 3) mean population age; 4) sleep disorder type; 5) timing of sleep disorder; 6) delirium assessment tool; and 7) type of surgery.

Sensitivity Analysis

The crude Risk Ratio of prospective cohort studies were computed and the random effects model was used to calculate the overall pooled estimate.

RESULTS

Study Selection

We identified 1, 238 citations (328 studies in the MEDLINE® database (PubMed), 939 in EMBASE, 86 in CINAHL, 266 in Web of Science and 76 in the Cochrane Library Database), and included 12 unique studies enrolling 1, 878 patients. The PRISMA flow diagram of the studies' selection is presented in figure 1.

Study Characteristics

All studies were reported between 2001 and 2015. They included seven prospective cohort studies[31, 32, 33, 34, 35, 36, 37] and five retrospective studies.[38, 39, 40, 41, 42] Nine studies had a sample size greater than or equal to 60.[32, 33, 35, 36, 37, 39, 40, 41, 42] The largest study was a retrospective cohort study involving 432 patients, [42] while the smallest was a prospective cohort study with 40 patients. [31]

Four studies specified obstructive sleep apnea (OSA) as the type of sleep disorder evaluated. [32, 34, 35, 39] However, the other studies did not explicitly specify the type of sleep disorder that was evaluated.[31, 33, 37, 38, 40, 41, 42, 43] Eight studies assessed pre-operative sleep disorder,[31, 32, 34, 35, 38, 39, 40, 43] three studies assessed sleep disorder immediately post-surgery but before the onset of POD,[37, 41, 42] and one study assessed sleep disorder occurring after the onset of POD.[33] Five studies evaluated orthopedic surgeries, [32, 36, 38, 39, 41] four studies evaluated cardiac surgeries,[31, 33, 35, 37] and others evaluated thoracic and non-cardiac surgeries.[34, 40, 42] Eight studies utilized the Confusion Assessment Method (CAM), a standardized evidence-based tool, [20, 21] to diagnose delirium, [31, 32, 34, 35, 36, 37, 40, 41] two studies used the Diagnosis and Statistical Manual of Mental Disorders (DSM-IV),[33, 42] and two studies utilized patient chart records and information obtained from caregivers to diagnose POD.[38, 39] Detailed characteristics of these studies are described in supplemental table 2.

Pooled Analysis

The Crude ORs were analyzed in this Meta-analysis. Yildizeli et al and Jeong et al did not report sufficient information to calculate crude ORs. Thus, data from this study was excluded in the analysis.[40, 42] A total of 1, 199 patients and 244 cases of POD were analyzed. The pooled odds ratio for the association between sleep disturbance and POD of 4.89 (95% CI: 3.45 to 6.94, p <0.001; I^2=0.0%, p=0.73) Fig 2a) was statistically significant. We next restricted our analysis to studies that evaluated sleep disorder before onset of POD. A total of 1, 096 patients and 225 cases of POD were analyzed. The pooled odds ratio for the association between pre-POD sleep disturbance and POD of 5.24 (95% CI: 3.61 to 7.60, p <0.001; I^2=0.0%, p=0.76; Fig 2b) was statistically significant.

Sub Group Analysis:

Sample Size—The pooled odds ratio for the association between sleep disturbance and POD of 3.37 (95% CI: 0.74 to 15.27, p =0.12; I^2=39.8%, p=0.19; Supplemental Figure 1) for the studies with less than 60 patients was not statistically significant.[31, 34, 38] However, the pooled odds ratio for the association between sleep disturbance and POD of 5.52 (95% CI: 3.72 to 8.17, p <0.001; I^2=0.0%, p=0.96; Supplemental Figure 1) for the studies with greater than 60 patients[32, 35, 36, 37, 39, 41] was statistically significant.

Study Design—The pooled odds ratio for the association between sleep disturbance and POD of 5.77 (95% CI: 3.82 to 8.73, p <0.001; I^2=0.0%, p=0.89; Fig 3a) studies[31, 32, 34, 35, 36, 37] was statistically significant. Similarly, the pooled odds ratio for the association between sleep disturbance and POD of 3.42 (95% CI: 1.39 to 8.44, p=0.008; I^2=9.1%, p=0.33; Fig 3a) for retrospective studies[38, 39, 41] was statistically significant.

Age (≥ 65 or ≤ 65)—The pooled odds ratio for the association between sleep disturbance and POD of 4.83 (95% CI: 3.00 to 7.78, p<0.001; I^2=0.0%, p=0.97; Fig 3b) for studies with median or mean patient age greater than 65 years [32, 34, 35, 36, 39, 41] was statistically significant. Similarly, the pooled odds ratio for the association between sleep disturbance and POD of 4.91 (95% CI: 1.35 to 17.86, p=0.02; I^2=47.9%, p=0.15; Fig 3b) for studies with median or mean patient age less than 65 years[31, 37, 38] was statistically significant.

Obstructive Sleep Apnea vs Unspecified Sleep Disorder—The pooled odds ratio for the association between sleep disturbance and POD of 4.75 (95% CI: 2.65 to 8.54, p <0.001; I^2=0.0%, p=0.85; Fig 4a) for obstructive sleep apnea [32, 34, 35, 39] was statistically significant. Similarly, the pooled odds ratio for the association between sleep disturbance and POD of 5.60 (95% CI: 3.46 to 9.07, p <0.001; I^2=0.0%, p=0.41; Fig 4a) for studies with unspecified types of sleep disorder[31, 36, 37, 38, 41] was statistically significant.

Timing of Sleep Disorder—The pooled odds ratio for the association between sleep disturbance and POD of 4.59 (95% CI: 2.82 to 7.48, p <0.001; I^2=0%, p=0.64; Fig 4b) for patients with pre-operative sleep disorder [31, 32, 34, 35, 36, 38, 39] was statistically significant. Similarly, the pooled odds ratio for the association between sleep disturbance and POD of 6.29 (95% CI: 3.55 to 11.17, p <0.001; I^2=0%, p=0.82; Fig 4b) for patients with post-surgical, but pre-POD, sleep disorder[37, 41] was statistically significant.

Delirium Assessment Tool—The pooled odds ratio for studies which utilized CAM screening tools [31, 34, 35, 36, 37, 41] for delirium assessment was 5.97 (95% CI: 3.93 to 9.08), p <0.001; I^2=0%, p=0.92, the study which utilized DSM-IV[32] had an OR of 4.33 (1.39 to 13.47), p =0.01 and two studies which made use of chart review or care giver assessment[38, 39] had a pooled OR of 2.21 (0.55 to 8.98), p =0.27; I^2=24.6%, p=0.25. Supplemental Figure 2

Type of Surgery—The pooled odds ratio for orthopedic/ non-cardiac surgeries[32, 34, 36, 38, 39, 41] was 3.92 (95% CI: 2.27 to 6.75), p <0.001; I^2=0%, p=0.79, while studies with cardiothoracic surgeries[31, 35, 37] had a pooled odds ratio of 6.77 (95% CI: 4.06 to 11.26), p <0.001; I^2=0%, p=0.78. Supplemental Figure 3

Sensitivity Analysis—We conducted a sensitivity analysis using risk ratios obtained from the prospective studies.[31, 32, 34, 35, 36, 44] The pooled risk ratio for the association between sleep disturbance and POD of 2.90 (95% CI: 2.28 to 3.69, p <0.001; I^2=0.0%, p=0.89) was significant. Supplemental Figure 4

Quality of Individual Studies and Publication bias.

Using the Newcastle-Ottawa form, all but the study by Koster et al. were defined as high quality (Supplemental Table 3a and 3b). The symmetrical nature of our funnel plot argues against observable publication bias (Supplemental Figure 5). We further assessed for publication bias by formal testing with both the Begg's and Egger's tests, and confirmed a null result for publication bias (P = .371 and .103, respectively).

DISCUSSION

Despite the heterogeneous design of available studies, we observed an association between sleep-disturbance and POD. Overall, patients with sleep disturbance were approximately 5 times more likely to develop POD compared to those without known history of sleep disturbance. Further sub-analyses suggested that these findings were conserved for OSA and unspecified types of sleep disturbances.

Consistent with our findings, Evans et al., in a pilot prospective study that used electroencephalogram recording to objectively study predictors of POD, found that diminished sleep time and increased sleep latency on post-operative day 1 is associated with increased incidence and severity of POD.[45] However, whether sleep disturbance is causal to POD to suggest that improved sleep hygiene would result in reduced incidence of POD, or whether sleep-disruption is an epiphenomenon that is associated with POD vulnerable brains, remains an open question.

Sedative drugs alter the level of arousal to achieve a behavioral state that closely approximates sleep. These drugs, most of which modulate the gamma amino butyric acid A receptor (GABAA), are instead associated with an increased incidence of POD and do not produce the neurophysiological oscillations of sleep. [46] GABAA receptor modulation is not a physiologically relevant mechanism for sleep promotion. [46, 47] Thus, it is not surprising that these medications are associated with neurophysiological dynamics such as

electroencephalogram frontal beta oscillations, frontal alpha oscillations, burst suppression and isoelectricity. [46] These oscillatory dynamics, which are fundamentally distinct from the oscillatory dynamics encountered during normal sleep, may reflect disruption in cognitive processing circuits. [46]

Zhang et al. performed a network meta-analysis of sedation strategies in mechanically ventilated patients and reported that dexmedetomidine is associated with a lower incidence of delirium.[48] However, the generalizability of this finding to non-mechanically ventilated post-surgical patients was unclear until Su et al. demonstrated that the administration of a prophylactic low-dose infusion of dexmedetomidine, an a2a adrenergic receptor agonist, resulted in significantly reduced incidence of POD in post-surgical non-cardiac patients.[49] Investigators from this research group also demonstrated this prophylactic low-dose infusion paradigm is associated with increased duration of stage N2 sleep, prolonged total sleep time, and increased sleep efficiency in non-mechanically ventilated post-surgical patients.[50] This finding is consistent with results from neurophysiological [51, 52, 53] and clinical polysomnography studies [54, 55] confirming that dexmedetomidine sedation closely approximates stage N2 sleep. Thus, pharmacological approximation of sleep may result in decreased incidence of POD.

To our knowledge, this is the first meta-analysis to assess the association between sleep disorder and POD. Key strengths of our meta-analysis include consistency of results, and lack of publication bias. We note that our meta-analysis was limited by the lack of randomized clinical trials, unspecified types of sleep disorder, and variability in metrics that were used to diagnose sleep disturbance and POD. Despite the limitation of variability in delirium assessment tools, CAM screening tools have been validated against the DSM-IV and found to be highly sensitive and specific.[56, 57]. We also stratified by sleep disorder to reduce any confounding by unspecified types of sleep disorder. Our present findings underscore the need for large randomized controlled studies of POD prevention that couple interventions such as intravenous dexmedetomidine,[48] physiologically relevant concentrations of oral melatonin,[58] and cognitive behavioral sleep therapy [59, 60] with objective sleep polysomnography metrics. These studies will enable causal inferences, and make clear the extent to which the incidence of POD may be modified by sleep in the peri-operative period.

CONCLUSION

We conclude that pre-operative sleep disturbances are likely associated with POD. Whether system-level initiatives targeting patients with pre-operative sleep disturbance may help modify this association remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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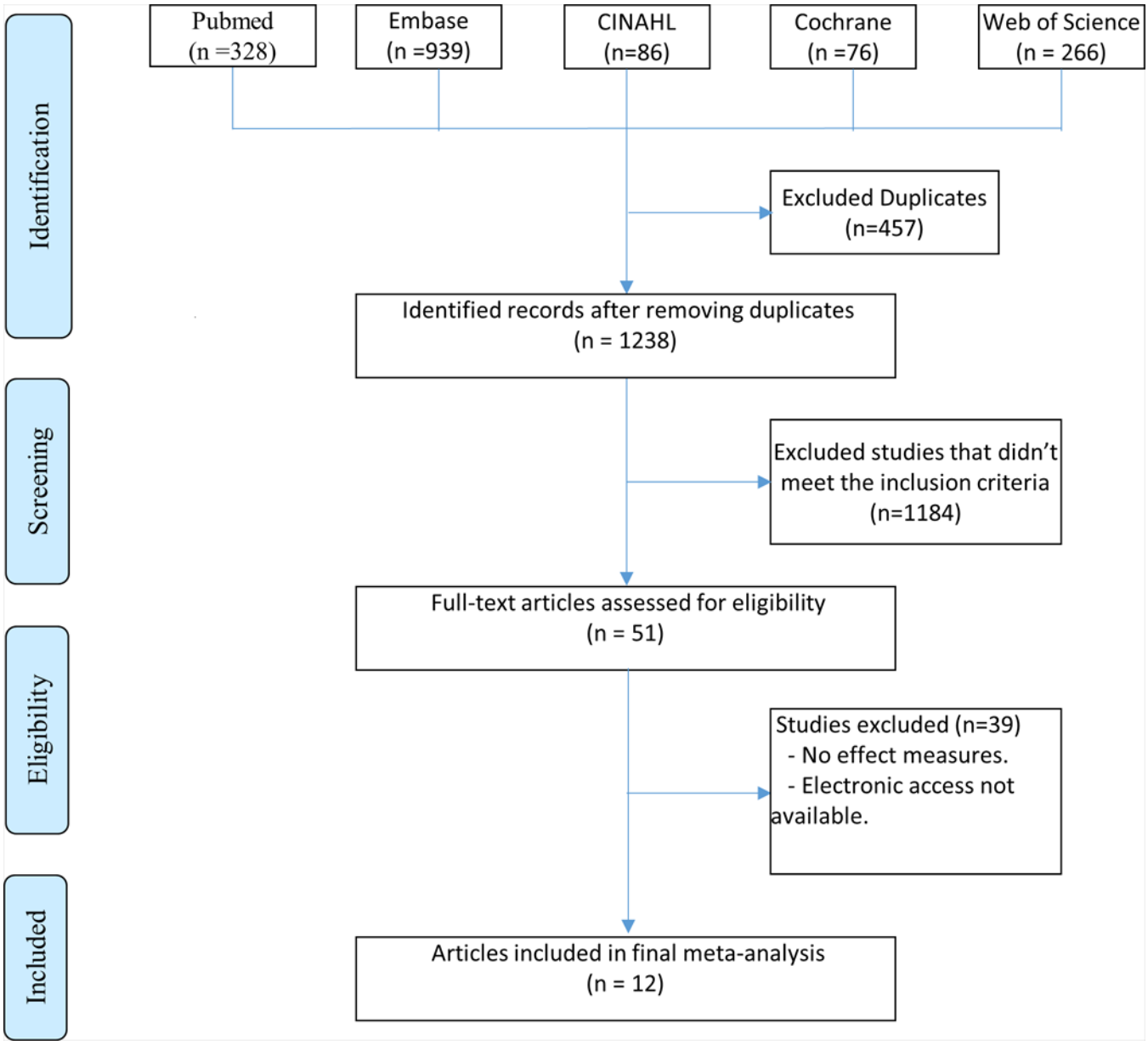

Figure 1.
PRISMA Flow Chart.

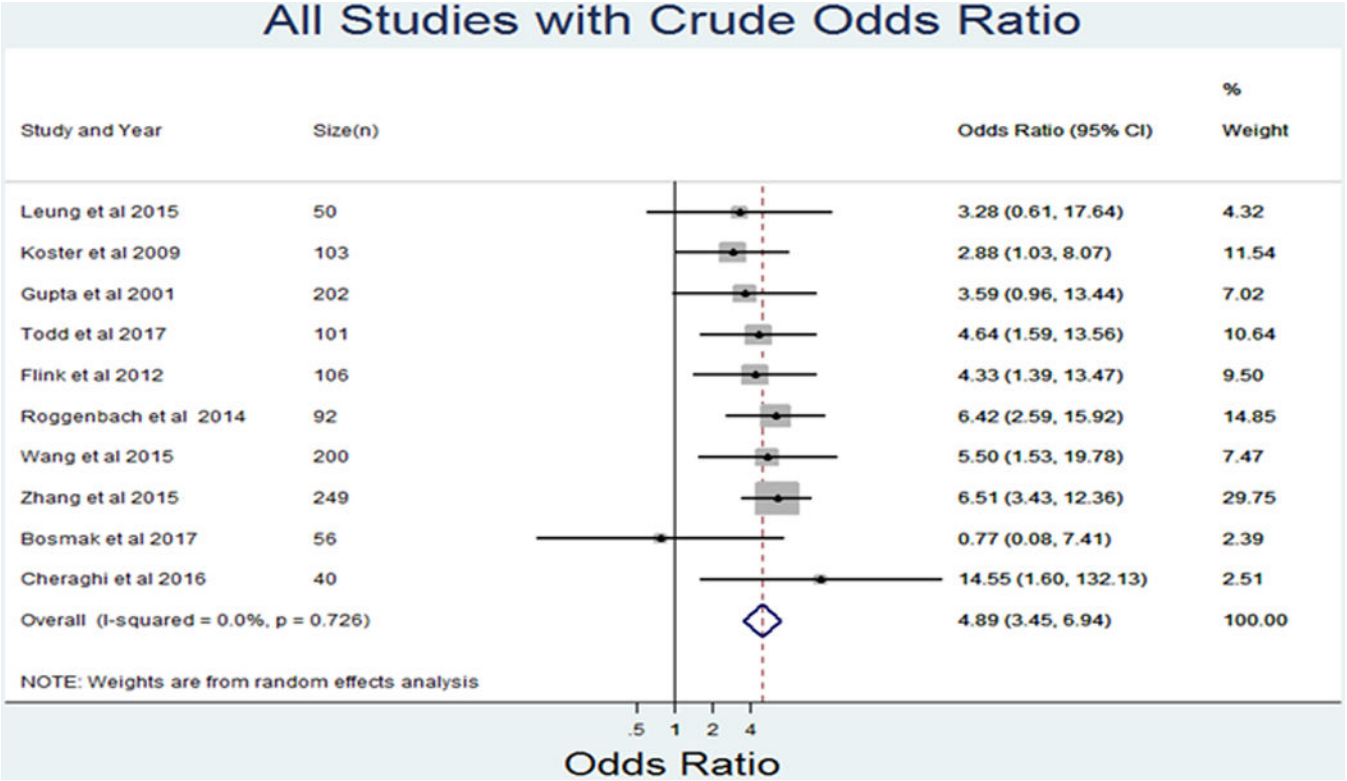

Figure 2a.
Forest plot showing pooled analysis of studies with crude odds ratio.

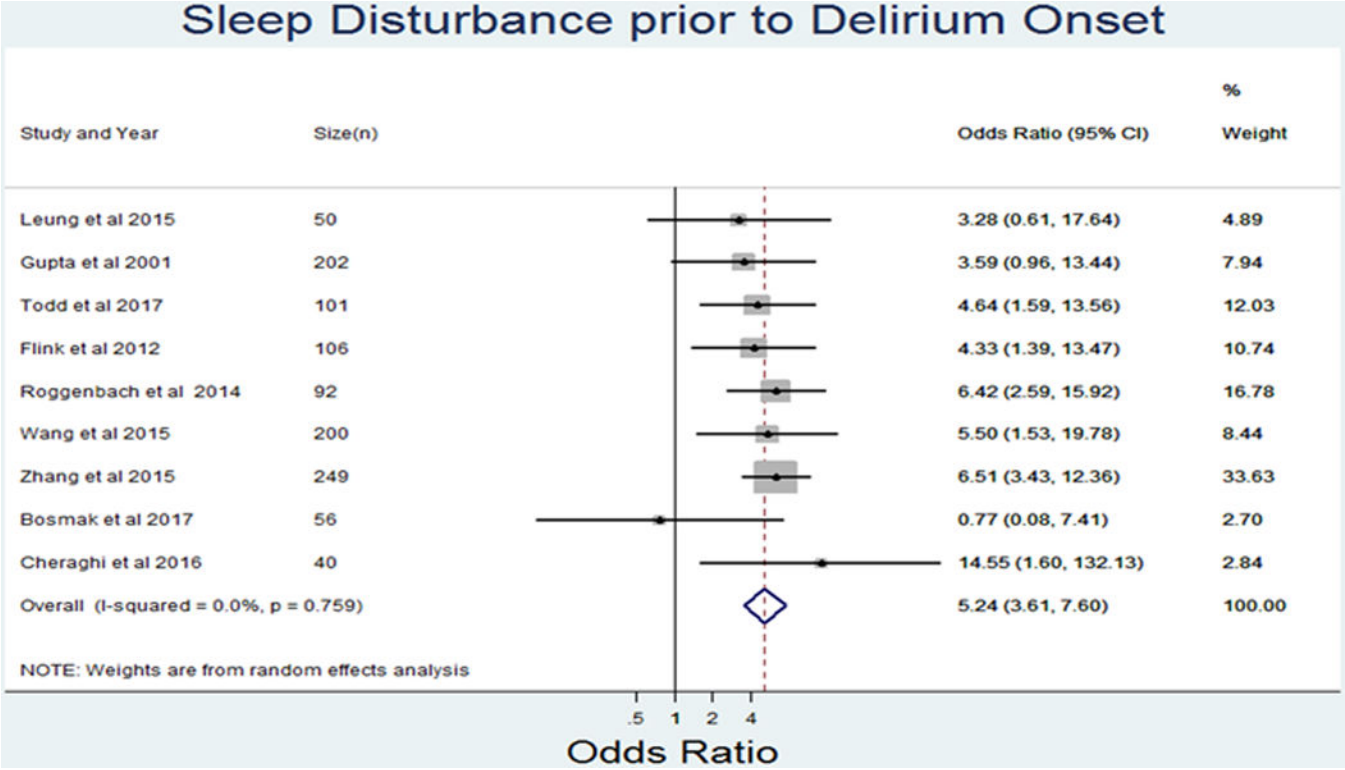

Figure 2b.

Forest plot showing pooled analysis after restricting to those with sleep disturbance before onset of delirium.

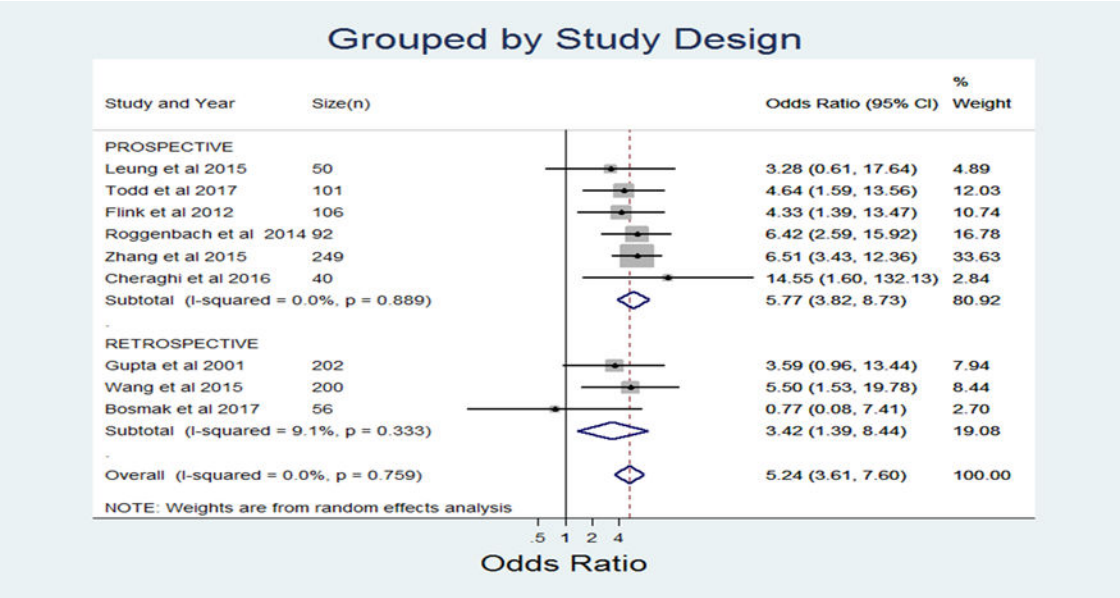

Figure 3a.

Forest plot showing pooled analysis of studies categorized into prospective and retrospective study design.

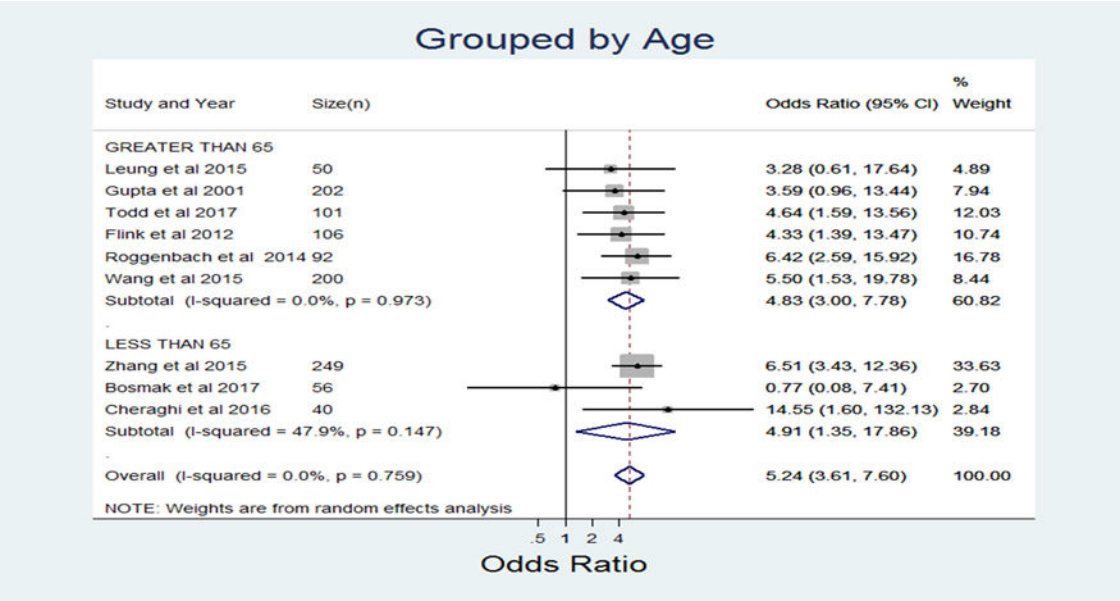

Figure 3b.

Forest plot showing pooled analysis of studies categorized into studies with median/mean age less than 65years and greater than or equal to 65 years.

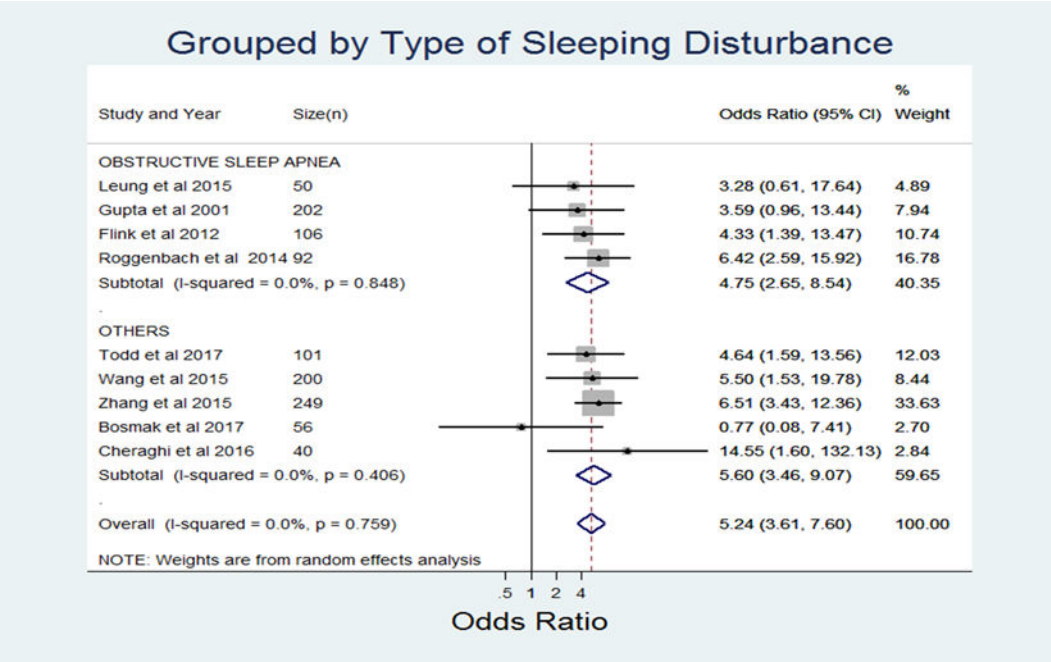

Figure 4a.

Forest plot showing pooled analysis of studies categorized into obstructive sleep apnea (OSA) and unspecified types of sleep disturbance.

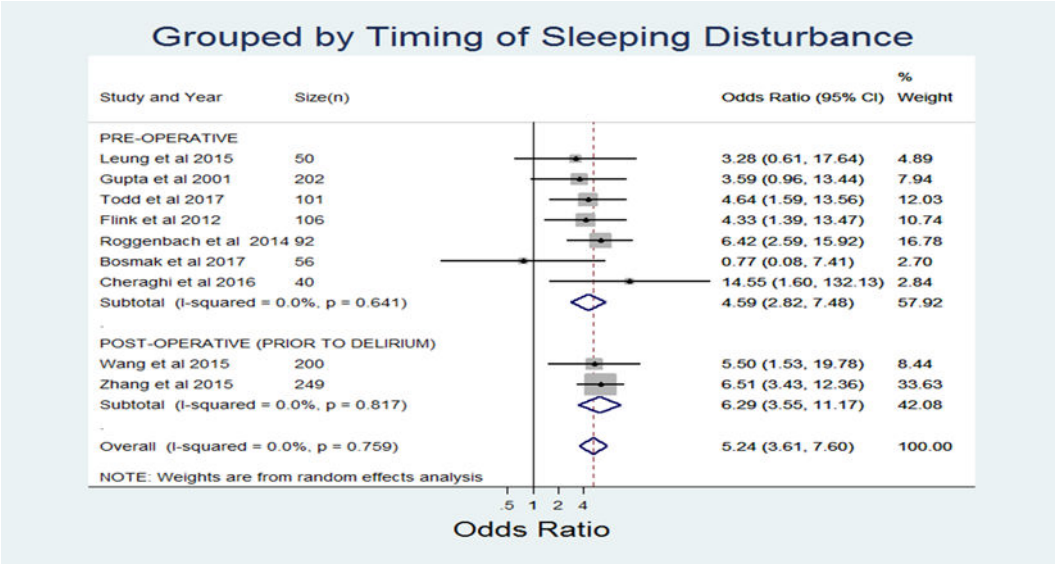

Figure 4b.

Forest plot showing pooled analysis of studies categorized into preoperative sleep disturbance and postoperative sleep prospective.