Review Article

Incidence of postoperative delirium in patients with preoperative and postoperative Obstructive Sleep Apnea Syndrome. A Systematic Review of the literature

ABSTRACT

Introduction: Clinical research has suggested that there might be a correlation between postoperative delirium (POD) and obstructive sleep apnea (OSA) syndrome. We aimed to assess the association between POD and OSA syndrome.

Methods: The electronic database PubMed was searched using combinations of terms for "Delirium," "Obstructive Sleep Apnea," and "postoperative delirium." Excluded were studies without comparison as well as cross-sectional studies, case series, and case reports. The search was conducted with restriction toward English or not to the date of publication.

Results: We included four studies in this review. In two of those studies, an association was found between POD and OSA syndrome. Pooled analysis showed a significant correlation between the two.

Conclusion: High-quality studies regarding the subject are rare and heterogeneous. However, despite the lack of high-quality studies regarding the subject, the ones that are performed well conclude that there is a correlation between POD and OSA syndrome. Future studies addressing the matter should be well set up controlled clinical trials to draw conclusions and be able to investigate modifiable factors that can be used in a standardized protocol.

Key words: Delirium, OSAS, postoperative

Introduction

Delirium is defined by the Diagnostic and Statistical Manual of Mental disorders (DSM) as an acute and fluctuating disturbance of the consciousness (i.e. reduced clarity of awareness of the environment) which occurs with reduced ability to focus, sustain, or shift attention,[1] a change in cognition (such as memory impairment, disorientation, language disturbance), or the development of perceptual disturbance that is not better accounted for by pre-existing, established, or evolving dementia. Moreover, the disturbance should develop over a short time (hours to days) and tends to fluctuate during the day.[1]

The pathophysiology of delirium remains unclear, but nowadays, it is widely presumed that the mechanism is multifactorial.

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Recent studies suggest that drug toxicity, inflammation, and acute stress responses can contribute to the development of delirium.[2] Other known risk factors for delirium are medication use, sensory impairment (loss of hearing or vision), immobilization, disturbances in the sleep-wake cycle, male sex, history of delirium, alcohol withdrawal, multiple comorbidities, and surgery.[2] The treatment of delirium depends on the underlying cause. Although there is no scientific tool to measure delirium several criteria and scales have been made to review the severity and categorize the disease.[3]

postoperative delirium (POD) is when the delirium occurs after surgery and anesthesia most of the times within 5 days following general anesthesia. POD differs from emergence delirium, which occurs immediately after waking up from anesthesia. POD is a common complication during the postoperative period and is associated with prolonged postoperative recovery, increased physical and mental morbidity and mortality.[4] The prevalence of POD in adult populations that have been exposed to surgery varies widely in different studies from as low as 1% to as much as 87% and is highly dependent on the type of surgery performed, the type of anesthetics being used, and patient population characteristics.[4]

Obstructive sleep apnea (OSA) is a disease characterized by sleep disturbance due to repeated airway collapses.[5] Thereby, the main risk factor is obesity.[6] The pathological mechanism of OSA is a narrowing of the airway due to the build-up of pressure on the airway or weakening of the surrounding tissue causing airway collapse. The accumulation of fat around the neck inflicts pressure on the airway when lying down during sleep and ultimately causes narrowing of the airway and hypoxia as a result. Other risk factors for the development of OSA are upper-airway abnormalities, male subjects, menopause, age, smoking, and alcohol abuse.[6] OSA has a prevalence of 3–7% in adults in the general population. In the subjects who undergo bariatric surgery, the prevalence of OSA can be as high as 77%.[6] Since the prevalence of OSA is so high in bariatric surgery, which is frequently performed nowadays, this systematic review aims to evaluate the incidence of pre- and POD in bariatric patients with OSA.

Methods

Search strategy

Subjects and methods

This literature review has been conducted in accordance with the The Journal of the American Medical Association guidelines[7] for articles about therapies and Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 checklist for Systematic Reviews [Appendix 1].

Literature search

The literature search was performed using PubMed and consisted of several components. The strategy was to include the components "Delirium" and "Obstructive Sleep Apnea" to find references regarding the relationship between delirium and OSA. Because of the interest in delirium after major surgery, the term "postoperative delirium" was added to the search strategy. We also searched for gray literature, and in addition, the reference lists in relevant publications were searched to detect eligible articles that were not identified through prior searches Appendix 2.

Study eligibility criteria

Included

This review included randomized controlled clinical trials, prospective and respective cohort studies, systematic reviews, and meta-analyses.

Excluded

This review excluded descriptive studies, case series, and case reports because of the lower level of evidence.

Types of participants

The studies on participants who were older than 18 years of age and who underwent surgery and screening for POD were included. Also, studies were included of those who compared the outcome of POD in the groups of patients with pre-existing OSA and patients without obstructive sleep apnea.

Obstructive sleep apnea indicators

Types of assessments for postoperative delirium and obstructive sleep apnea

POD can be assessed through the Delirium Rating Scale, Revised (DRS-R-98)[8] and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[9]

Study selection and data extraction

Two reviewers (SD and BT) independently screened titles and abstracts based on the inclusion and exclusion criteria. Subsequently, the same reviewers independently checked the remaining full-text reports for eligibility. After completing the definitive inclusion of articles, data from full-text articles were extracted independently. In all the stages, disagreements were solved by discussion or by consulting an independent third reviewer (DF). Data on the outcomes were collected and analyzed.

Assessment of risk of bias

Two reviewers (SD, BT) independently assessed the risk of bias for methodological quality of each included study using the Cochrane Collaboration's Risk of Bias (RoB). Each study

was judged on selection bias, performance bias, detection bias, attrition bias, reporting bias, and confounding.

Results

Study selection

The final search strategy yielded 36 references. The studies were included if there was an assessment done for POD. The studies were included if there was an assessment done for OSA or if the medical records reported OSA or if the patients themselves reported to suffer from OSA before and after surgery. The exclusions were done because of not diagnosed or self-reported OSA, age below 18, dementia, and other preoperative existing mental disorders. Furthermore, studies not available in English were excluded. The search strategy is outlined.

Study characteristics of included studies

Four studies, including 8,534 subjects, and one meta-analysis including 12 studies, were included in this review. All the studies were performed in the United States and the studies were published in English. Three out of four studies compared a group of subjects with OSA to a group without OSA. One study compared peri-operative continuous positive airway pressure (CPAP) to routine care to see if CPAP can help in preventing POD with OSA. The primary hypothesis of one study was to examine the molecular markers in POD. The primary hypothesis of the other three studies was related to OSA and POD. The study by Flink *et al*.[10] investigated whether any of the pre-existing medical conditions contributed to POD. The study by Nadler *et al*.[11] tested if the use of CPAP could prevent POD in patients who are at risk of OSA. And the study by King *et al*.[12] tested if there was an association between preoperative sleep apnea and POD. The study done by Wang *et al*.[13] investigated if thoracic surgery patients were at a high risk for OSA and POD. The meta-analyses conducted by Fadayomi *et al*.[14] aimed to assess the association between preoperative sleep disturbance and POD.

Characteristics of subjects in the individual studies

The study conducted by Flink *et al*.[10] described the results of 106 patients who had undergone elective knee surgery. Of the 106 subjects, 15 had OSA, and of these, 8 patients (53%) experienced POD versus 19 (21%) out of 91 subjects who experienced POD without having OSA. The DSM-IV criteria for delirium were used to diagnose POD. To determine if a subject has OSA, medical records were used as well as patient interviews. Having a delirium was expressed in a DRS-R-98 severity score. Age was expressed as mean in years (+SD). Several other risk factors for developing delirium were evaluated. Dementia was evaluated with the Minimal Mental State Exam score and by reviewing medical records.

The study conducted by Nadler *et al*.[11] describes the results of 135 subjects of whom 114 completed the study. The study groups were divided into CPAP and NON-CPAP groups. Delirium was equally common in both groups. OSA was described using the Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference and Gender score.[15] Age was described using mean years (+SD). The assessment for delirium was done using the DRS-R-98[8] diagnostic tool.

King *et al*.[12] described a cohort of 7,792 subjects admitted to the intensive care unit after surgery. The evaluation of OSA included medial history, self-reported OSA, self-reported adherence to CPAP, and after April 2014, the STOP-BANG questionnaire was included. POD was assessed with the CAM-ICU.

Wang *et al*.[13] described a cohort of 126 patients admitted to the ICU after undergoing thoracic surgery. The assessment for OSA was done using the STOP-BANG questionnaire and the CAM-ICU was used to assess delirium.

Fadayomi *et al*.[14] performed a meta-analysis of the available literature. They described the results of 12 included studies. The included studies used different methods for the assessment of OSA and POD, with STOP-BANG scores and the CAM-ICU as the most prevalent methods used.

Risk of bias and methodological quality

The studies conducted, except for one,[14] had a high risk of performance bias since none of them blinded the subjects to the intervention. However, Nadler *et al*.[11] did blind the assessors. The subjects cannot be blinded in most cases due to the nature of the intervention.

In the study conducted by Flink *et al*.[10] also, no randomization was performed. Nadler *et al*.[11] did perform computerized randomization. Wang *et al*. also performed randomization.

The main outcomes were clearly described in all the studies. The confounders were unclear in most studies. The selection bias was unclear, but the risk of selection bias was high in two out of four studies since they were retrospective studies. The risk of detection bias was high in two[10,11] studies since there was no double-blinding. The risk was also high in all studies. Because blinding of the subjects was not possible due to the nature of the intervention. The risk of attrition bias was high in three[10,11,13] of four studies due to the subjects enrolled not completing the study.

Fadayomi *et al*.[14] performed Begg's and Egger's tests for publication bias and confirmed a null result for publication bias, ($P = 0.371$ and 0.103, respectively)

Heterogeneity between the studies was high due to different research questions and methods of testing for obstructive sleep apnea syndrome (OSAS) and different cut-off points. Only Nadler *et al*.[11] described a formal power analysis. It is not possible to assess whether the number of included subjects was sufficient for a powerful statistical analysis in the remaining studies.[10,13] The methodological quality of the included studies is outlined in Table 1.

Results of the individual studies

Flink *et al*.[10] found that the incidence of POD was higher in the OSA group (53,3%) than in the patients without OSA (20. 9%) ($P = 0.0123$, odds ratio = 4.3, 95% CI 1.2–15.8). In their study, there was no difference found in other baseline medical conditions between delirious and non-delirious patients. When the patients with OSA and without OSA were compared, the OSA group was younger and suffered more comorbidities.

The study conducted by Nadler *et al*.[11] found that the incidence of POD was the same in the groups which received CPAP therapy compared with the group which received only routine care (OR = 1.36 [95% CI 0.52–3.54], $P = 0.53$). The investigators did find that the severity of preoperative apnea is associated with the severity of POD ($P = 0.0002$). They did not find CPAP therapy shortly before surgery to have any effect on the incidence of POD.

The study by King *et al*.[12] found that the patients with OSA had a lower incidence of POD than patients without OSA, but after adjustment, this difference was not significant.

Wang *et al*.[13] found that there was no significant difference in the incidence of delirium between the high-risk group and low-risk group for OSA ($P = 0.7$). There was also no difference found between the high- and low-risk group for the duration of POD.

The systematic review by Fadayomi *et al*.[14] found that the pooled odds ratio for the association between sleep disturbance POD was 5.24 (95% CI 3.61–7.60; $P < 0.001$ and I2 = 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 2.28–3.69; $P < 0.001$ and I2 = 0.0%; $P = 0.89$). The odds ratio associated with OSA, and unspecified types of sleep disorders were 4.75 (95% CI 2.65–8.54; $P < 0.001$ and I2 = 0.0%; $P = 0.85$) and 5.60 (95% CI 3.46–9.07; $P < 0.001$ and I2 = 0.0%; $P = 0.41$), respectively.

Discussion

The association between OSA and POD has been a subject of discussion in recent years. However, the amount of evidence provided for such an association is limited and of low quality. The first point of discussion is the fact that a meta-analysis was not possible due to the high heterogeneity between the studies. The assumption for meta-analysis could therefore not apply.

In 2020, King *et al*.[12] found no association between preoperative OSA and POD so the existence of an association is questioned and uncertain. They also concluded that it is unlikely that there is an intervention that may help to reduce the incidence of POD after surgery with preoperative existing OSA. Their cohort is the largest that was encountered in this research, but it was another retrospective observational study, so there was no natural experiment to give a strong causal implication. Moreover, they included a wide array of diverse surgical procedures in a single-center cohort setting. This type of setting is likely to be different elsewhere, so caution is advised when generalizing these findings. They also report that incomplete data and the observational nature of their study could explain their null findings.

In 2017, a systematic review by Fadayomi *et al*.[14] of the available literature in PubMed, Embase, and other medical databases concluded that there was likely an association between sleep disturbances and POD. The authors included 12 studies, but only 4 of those studies specified OSA as the type of sleep disorder evaluated. The types of assessment

Table 1: Methodological quality of included studies

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Confounding	Grade Score
Flink *et al*.[10]	-	+	-	?	-	?	Moderate
Nadler *et al*.[11]	-	+	?	?	-	?	Moderate
Wang *et al*.[13]	-	-	-	-	-	?	high
King *et al*.[12]	+	+	-	-	-	-	Moderate
Fadayomi *et al*.[14]	-	-	-	-	-	?	High

- = low risk of bias, + = high risk of bias,? = unclear risk of bias

Grade, Grading recommendations assessment development and evaluation; High, True effect lies close to the estimate of the effect; Moderate, True effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low, True effect may be substantially different from the estimate of effect; Very low, True effect is likely to be substantially different from the estimate of effect

for determining OSA and POD also differed in the included studies. Overall, they reported heterogeneity between the studies evaluated and concluded that there was an association between preoperative sleep disturbances and POD. They also reported that if there was some intervention that helps to reduce the incidence of POD, it is yet to be determined.

Nadler *et al*.[11] mentioned that their results might be interfered with because of the low adherence to the CPAP therapy because of discomfort or other reasons. This could mean that the people who did adhere to the CPAP therapy were more likely to have a decreased risk for POD.

Flink *et al*.[10] did find an association between OSA and POD. This first prospective study employing validated measures of delirium to identify an association between pre-existing OSA and POD found a more-than-fourfold increased risk for POD. Since this is the only prospective study researching this matter, it is quite remarkable that they found an association whereas other retrospective studies did not. The authors mentioned that their sample size was small, but since this is the only prospective study with published results to date, the findings by the authors were of significant clinical importance and deserve replication in larger numbers. Another limitation to their findings was that the patients with OSA had significantly more comorbidities that could increase the risk for delirium in those patients. Although the authors took several predisposing factors for delirium into account, like dementia, they did not account for a history of stroke and electrolyte disturbance which are also known predisposing factors for delirium.

Wang *et al*.[13] only found that patients with a high risk of OSA had a longer duration of POD. There was no difference in the incidence between the high- and low-risk groups.

Although some studies used the same methods for the assessment of POD and OSA, they did differ in a lot of other factors, like the time of assessment and the scale used for assessing POD. Overall, the results yielded by the studies were not of high quality and convincing enough that there was an association between OSA and POD. Due to the heterogeneity between the studies, it was hard to draw conclusions about the association between OSA and POD. This is due to the difference in the study sample sizes, the different methods for assessment used, and the different key questions used in the studies. And because some studies included that the primary aim of the studies was never to find an association between OSA and POD. Another interesting factor in this review is that none of the studies hold into account what kind of anesthetics was given to the subjects. They all report that the patients received general anesthesia but did not specify the types of medication used. This might be a factor that contributes to the different findings of the studies because some medications may have a longer half-life than others, meaning they could contribute to a longer duration of sedative state, and therefore, to the severity and/or duration of POD.

Considering the described heterogeneity and overall quality of the included studies, it is hard to draw conclusions.

To determine whether there is in fact an association between OSA and POD, larger prospective randomized clinical trials are needed with less heterogeneity between studies. The same is applicable to whether there is a modifiable intervention to prevent POD in the case of pre-existing OSA.

Conclusion

The recommendation for studies regarding the matter in the future is to study in a large cohort the association between pre-existing OSA and the incidence of POD. Because it is assumed that the pathophysiological mechanism of delirium is multifactorial, other factors such as type of anesthesia, kind of surgery, duration of surgery, and other factors that might have an influence on POD have to be considered.

If an association is found between the two in a large Randomized Clinical Trial, then it should be investigated if there is a modifiable factor to prevent the POD in these OSA patients and how such an intervention can be implemented in a standardized protocol.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Appendix 1: PRISMA checklist

Section/Topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both *Comment:* *Title: Incidence of postoperative delirium in patients with preoperative and postoperative Obstructive Sleep Apnea Syndrome. A Systematic Review of the literature*	Page 1. Line 1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number *Comment:* *We performed a structured summary including all the mentioned aspects.*	Page 2. Line 32-48
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. *Comment:* *The rationale is described in detail in the Introduction.*	Page 3. Line 65-101
Objectives	4	Provide an explicit statement of questions being addressed with reference to the participants, interventions, comparisons, outcomes, and study design (PICOS). *Comment:* *This systematic review aims to evaluate the incidence of pre- and postoperative delirium in bariatric patients with OSA.*	Page 3. Line 98-101
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including the registration number. *Comment:* *The protocol can be retrieved electronically by the first author.*	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as the criteria for eligibility, giving rationale. *Comment:* *In Subjects and Methods, we described in detail the search strategy and included databases, the study eligibility criteria (the types of studies included, the included and excluded participants, and the inclusion and exclusion criteria, and the included test methods).*	Page 4. Line 105-148
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. *Comment:* *The literature search was performed using PubMed and consisted of several components. The strategy was to include the components "Delirium" and "Obstructive Sleep Apnea" to find references regarding the relationship between delirium and obstructive sleep apnea. Because of the interest in delirium after major surgery, the term "post-operative delirium" was added to the search strategy. We also searched for gray literature, and in addition, the reference lists in relevant publications were searched to detect eligible articles that were not identified through prior searches.*	Page 4. Line 111-117
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. *Comment:* *Details of the flowchart and entire search strategy are described in Appendix 2*	Appendix 2:
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in a systematic review, and, if applicable, included in the meta-analysis). *Comment:* *Two reviewers (SD and BT) independently screened titles and abstracts based on inclusion and exclusion criteria. Subsequently, the same reviewers independently checked the remaining full-text reports for eligibility. After completing, the definitive inclusion of articles, data from full-text articles were extracted independently. In all stages, disagreements were solved by discussion or by consulting an independent third reviewer (DF). Data on the outcomes were collected and analyzed.*	Page 5 Line 142-148
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. *Comment:* *After completing the definitive inclusion of articles, data from full-text articles were extracted independently. In all stages, disagreements were solved by discussion or by consulting an independent third reviewer (DF). Data on the outcomes were collected and analyzed.*	Page 5 Line 143-148

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Appendix 1: Contd...

Section/Topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. *Comment:* *Appendix 2 describes in detail the included search terms and the included databases.*	Appendix 2
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. *Comment:* *The risk of bias and our attempt to reduce the risk of bias in the individual studies was described in both the Subjects and Methods section and the Results.*	Page 5. Line 150-154
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Comment:* *Best-evidence synthesis was described in the Subjects and Methods section. This systematic review was a qualitative synthesis of the available evidence. In view of the heterogeneity of the target population, the variability of study objectives, and differences in methodological quality, a meta-analysis could not be performed.* *In the Results, we described in detail our findings about our research question.*	Page 7. Line 248-266
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. *Comment:* *The performed best-evidence syntheses were described in the Subjects and Methods section.* *In the Results, we described in detail our findings. This systematic review was a qualitative synthesis of the available evidence. In view of the heterogeneity of the target population, the variability of study objectives and differences in methodological quality, a meta-analysis could not be performed.*	Page 6-7 Line 189-286

Section/Topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of the risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). *Comment:* *The risk of bias and our attempt to reduce the risk of bias in the individual studies was described in both the Subjects and Methods section and the Results.*	Page 7 Line 157-162 Table 1 Page 7 Line 244 – 262 Table 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. *Comment:* *Not applicable.*	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. *Comment:* *Appendix 2 shows in detail the flow of information through the different phases of the systematic review.*	Appendix 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. *Comments:* *Presented in the Results section*	Page 7-8 Line 264-286
Risk of bias within studies	19	Present data on the risk of bias of each study and, if available, any outcome level assessment (see item 12). *Comment:* *The risk of bias and our attempt to reduce the risk of bias in the individual studies was described in both the Subjects and Methods section and the Results.*	Page 7 244-262 Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. *Comment:* *Details about the individual studies are described in the Results.*	Page 8 Line 195 – 211 Table 3. Page 2

Contd...

Appendix 1: Contd...

Section/Topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. *Comment:* *This systematic review was a qualitative synthesis of the available evidence. In view of the heterogeneity of the target population, the variability of study objectives, and differences in methodological quality, a meta-analysis could not be performed. The results of the studies are described or depicted in the Results and in Table 1*	Page 6 Line 189-286 Table 1
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15). *Comment:* *The risk of bias and our attempt to reduce the risk of bias in the individual studies was described in both the Subjects and Methods section and the Results.*	Page 7 Line 244-262 Table 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). *Comment:* *Not applicable.*	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers). *Comment:* *The main findings and their implications are described in the Discussion. The Discussion described the short the included studies, explanation of the inconsistent Results.*	Page 9 Line 329-394
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment:* *Limitations of the review were described in detail.*	Page 9 Line 331-394
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. *Comment:* *We described that for the future methodological well-conducted randomized controlled trials in larger groups of subjects with more equal distribution and extensive measurements methods are necessary to investigate the pain sensitivity and pain perception in obese subjects vs. non-obese subjects.* *In addition, we were advised to study the unknown variables of influence to pain sensitivity and pain perception in obese subjects.*	Page 10 Line 397-403
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); the role of funders for the systematic review. *Comment:* *This systematic review was performed without any funding and the authors have no disclosure of interest. The authors have no disclosure of interest regarding the systematic review.*	Page 1 Line 24-26

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6 (6): e1000097. doi: 10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2: Search Strategy

Clinical question

Component	PICO
Patient/population	Patients who undergo surgery
Intervention	Patients with OSA
Comparison	Non-OSA patients
Outcome	Postoperative delirium

OSA=Obstructive sleep apnea

Literature Search in PubMed

Component 1: Delirium

Search strategy for component 1:

"'Delirium" '[MeSH Terms] OR "'Delirium" '[Tiab] OR "'delirium" '[Tw] OR "'Postoperative delirium" '[Tw] OR "post-operative delirium"[Tiab]

Component 2: Obstructive sleep apnea

Search strategy for component 2:

"'Sleep Anea, Obstructive" "'[MeSH] OR "'Obstructive Sleep Apnea" "'[Tiab] OR "'Obstructive sleep apnea" "'[Tw] OR "OSA"[Tw] OR "OSAS" [Tw] OR OSA[Tiab] OR OSAS [Tiab]

Combined strategy

('"Delirium"'[MeSH Terms] OR '"Delirium"'[Tiab] OR '"delirium"'[Tw] OR '"Post-operative delirium"'[Tw] OR "post-operative delirium"[Tiab]) AND ('"Sleep Anea, Obstructive"'[MeSH] OR '"Obstructive Sleep Apnea"'[Tiab] OR '"Obstructive sleep apnea"'[Tw] OR "OSA"[Tw] OR "OSAS" [Tw] OR OSA[Tiab] OR OSAS [Tiab])

Number of references: 37

Date 16-05-2020

The number of articles yielded with this strategy is not very high, but the relevance of the articles found was good.