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ORIGINAL RESEARCH **PERIOPERATIVE MEDICINE**

Association of obesity with postoperative hypoxia: A meta-analysis

Yang Ting, Muhammad Saqib Mudabbar, Liu Bin

Author affiliation:

Department of Anesthesiology, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu City, Sichuan Province, People's Republic of China.

Correspondence: Liu Bin, Department of Anesthesiology, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu City, Sichuan Province, People's Republic of China; E-mail: liubinhxyy@163.com; Phone: +86-18980601540

Abstract
Post-operative hypoxia is a fairly common clinical complication with severe consequences that can result in permanent organ damage, increased morbidity, increased cost, poor prognosis, and increased fatality. To effectively understand the factors that contribute to such a disease, we conducted a study to determine if obesity is a risk factor of post-operative hypoxia. A thorough search for articles was conducted on various databases. A total of 15658 potential studies were identified out of which 8 were included in this meta-analysis. Data was extracted and analyzed which included 2500 subjects; 1265 subjects in the obese group, and 1235 subjects in the lean group. The combined effect size was 0.19. The results showed that the incidence of post-operative hypoxia in obese was not significantly higher than the lean patients. In conclusion, the meta-analysis reveals that there is no significant correlation between obesity and postoperative hypoxia.

Key words: Meta-analysis; Hypoxia; Obesity; Postoperative; Risk factor

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1. Introduction
Oxygen is necessary for the survival of cells and tissues in our body. Without it, our cells would be unable to perform their normal functions. This inadequate oxygen supply would lead to a condition known as hypoxia. Hypoxia is a condition in which the body or a region of the body is deprived of adequate oxygen supply at the tissue level. During surgery, the body of a patient undergoes several kinds of trauma and the effects of these traumas can be diverse. Hypoxia is a rather common post-surgically. Obesity is could be one of the most significant predisposing factors of post-surgical hypoxia. One of the main reasons is that there are several mechanisms that associate obesity with respiratory dysfunction which would result in an overall increase in the work of breathing. Many studies have shown that the work of breathing is noticeably higher in obese patients,[1,2] and in morbidly obese patients; the respiratory drive is blunted.[3] Some of these mechanisms have been recognized. A decrease in the functional residual capacity observed in obese patients, for instance, is one of the chief mechanisms that lead to the increased work of breathing.[4] Besides, a person's posture or position can also result in difficulty breathing, such as in a supine position an obese person would experience a significant increase in the total respiratory resistance.[5] Not only these but several other factors link obesity with respiratory dysfunction which includes an increase in the collapsibility of the larynx, upper airway inflammation, neurohormonal influences that lead to sleep disorders, and impairment in the function of respiratory muscles.[6]

Other studies, including the changes in lung volumes results in a reduced functional residual capacity, ventilation/perfusion mismatch, increased total respiratory resistance, and diminished thoraco-pulmonary compliance still plays a crucial role even during mechanical ventilation. After surgery with cardiopulmonary bypass, obese patients experience the combination of a pre-existing lung dysfunction (mainly represented by a volume reduction) with the perioperative damage that acts as an extra factor determining the loss of ventilating areas. The main pattern of this lung profile is extra-vascular lung water accumulation, triggered by the increased permeability of the alveolo-capillary membrane, hemodilution with fluid overload, and adverse effects of allogeneic blood product transfusions (including transfusion-associated lung injury).

Another study found that postoperative hypoxemia in an obese patient is multifactorial such as decreased chest wall compliance, upper airway obstruction, and central apnea. Decreases in vital capacity, functional residual capacity, and thoracic compliance are observed in these patients.[7] These effects are most significant in the horizontal position[8]: the position used for all transfers into the post anesthesia care unit.

Obesity also leads to anatomical changes to the upper respiratory tract. The oropharyngeal sector is reduced, and the laryngeal muscle tone is diminished. For this reason, obesity seems to be a major risk factor for obstructive sleep apnea syndrome. During the postoperative period, the risk of obstruction of the upper airways leading to hypoxemia is significant.[9]

However, some of these factors like respiratory drive, work of breathing, and upper airways conditions in patients could be because they are narcotized, paralyzed, and mechanically ventilated patients in which case these are the factors that should be taken into account.[10]

1.1. Rationale

The prevalence of hypoxia is quite common, yet with current interventions there is much room for improvement. Patients that suffer from hypoxia generally need to be oxygenated which not only can go unnoticed but sometimes might be considered unnecessary when it is. Hypoxia is a serious problem and should be dealt with care. Despite its health-care-related economic burden, morbidity, and detrimental effects on quality of life, we haven't yet fully understood the risk factors of this disease. Therefore, to achieve this goal, potential risk factors ought to be identified and treated promptly to prevent it or at least retard the progression of hypoxia in post-surgical patients, saving a patient's life from serious organ damages or even death.

1.2. Objective

To determine if obesity is a potential risk factor of post-surgical hypoxia.

2. Methodology

A comprehensive search of literature databases was undertaken including but not limited to PubMed, Ovid, Embase, and Wiley. To search the following MeSH terms were used, "Hypoxia"[MeSH], "Postanesthesia Nursing"[MeSH], "Postoperative Period"[MeSH], "Association"[MeSH] in different combinations using BOLEAN logic. A total of 15658 potential studies were identified and lists of citations were made for removal of duplicate studies. A total of 23 duplicate articles were found. After the removal of duplicate studies, an abstract assessment process was carried out. The exclusion criteria were to remove all studies that did not include obesity as one of the studied risk factors. Also, studies that didn't have the data clearly provided were excluded. Studies that were related to obesity as a risk factor of post-surgical hypoxia were considered eligible. 15564 were excluded and a list of 73 articles was made for full-text assessment, studies that included other variables, such as diseases and treatments were also included, in the end, articles that only had complete and comparable data were included a total of 8 studies were included in the thesis while 23 were excluded for having data that could not be compared. In order to reduce observation bias two independent individuals searched and screened the articles and arrived at the same result. There were no language restrictions imposed.

1.3. Literature search results

1.3.1. Information of included literature

A total of 73 references were initially retrieved for full-text assessment according to the study design. 31 references were finally included, all of which were in English, these had the data for obesity and postoperative hypoxia. The studies that had data taken at different times, using a different time, the exact values were not given, or a binary value was assigned were incomparable to the rest of the studies and thus were excluded. In the end we included 8 studies which made the observations at the same time, using comparable values. (Figure 1) Adults were predominant in these studies. The total number of candidates in the studies was 2500.

1.3.2. Risk of bias assessment

Five studies mentioned allocation concealment. Three studies were single-blind to the subjects.

3. Results

Several studies suggest that anesthetic agents limit the inspiratory flow as a result of a depressive effect on the muscles of the upper respiratory tract. Here are the studies we included (Table 1):

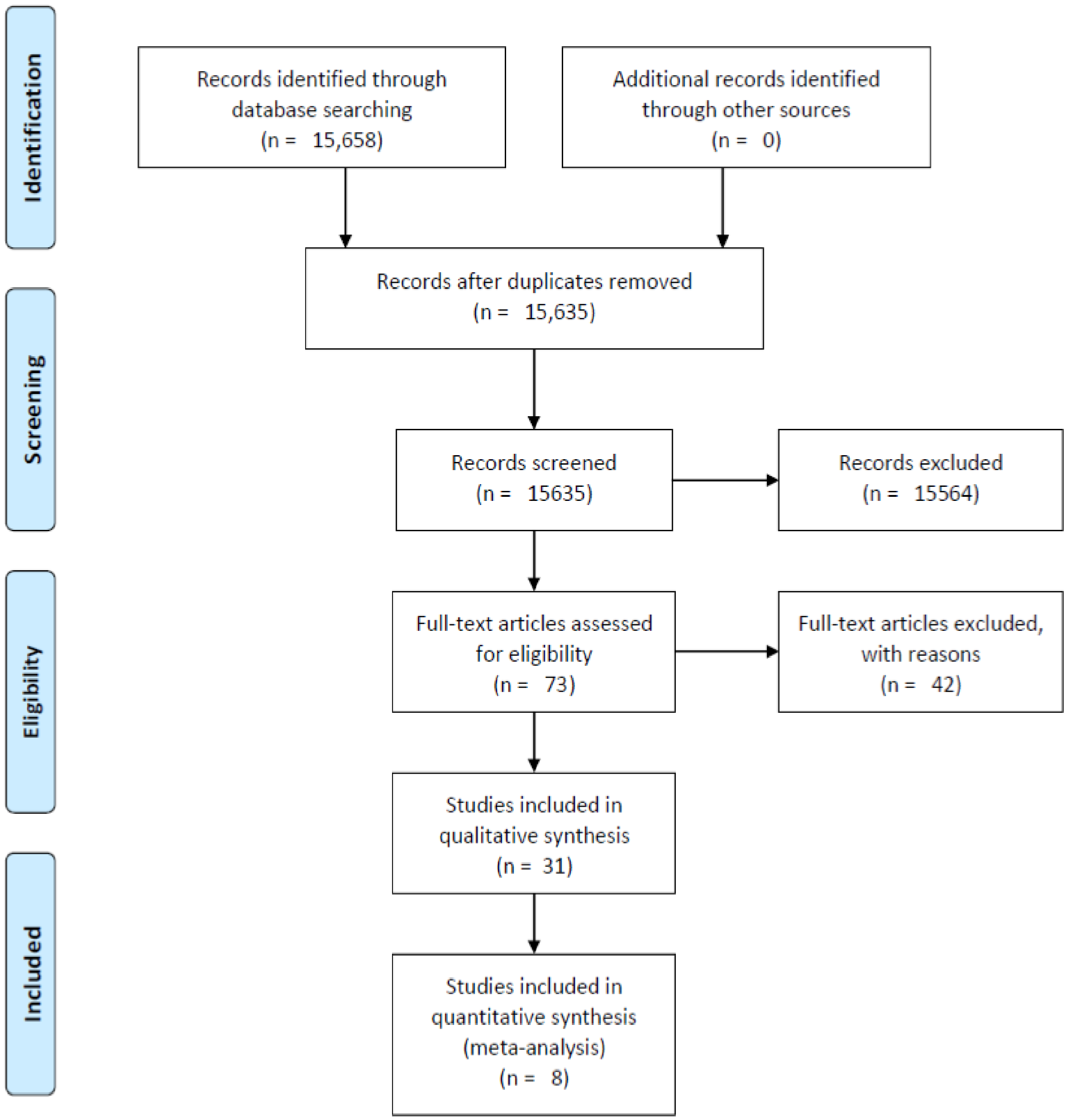

Figure 1: PRISMA consort flow diagram

Table 1: The salient results of the enrolled studies

	Author	Variables studied	N = 2500	P-value or Outcome	Interpretation
1.	Pelosi P et al.	Obesity, hypoxia, respiratory mechanism	20	A reduced pulmonary oxygenation index (PaO_2/PAO_2 ratio).	Reduced oxygen due to decreased lung capacity and increased work of breathing results in postoperative hypoxia.
2.	Sampson MG et al.	Neuromechanic-al breathing, hypoxia, CO_2	10	The decreased neuromuscular responsiveness to carbon dioxide among the group with former obesity-hypoventilation syndrome when compared with that in the group with simple obesity is a consequence of a blunted neural (central) drive, and not due to any apparent worse mechanical limitations.	An acute extra load on the respiratory system produces the obesity-hypoventilation syndrome in those obese persons who have truly blunted central hypercapnic responses.
3.	Yap JC et al.	Posture, respiratory mechanics, obesity, hypoxia	14	Seated mean total lung capacity was smaller in obese than in control (82 vs. 100% of predicted); the ratio of functional residual capacity (FRC) to total lung capacity averaged 43% in obese and 61% in control ($P < 0.01$). Total respiratory resistance (Rrs) at 6 Hz seated was higher in obese (4.6 $cmH_2O.l\text{-}1.s$) than in control (2.2 $cmH_2O.l\text{-}1.s$; $P < 0.001$); total respiratory reactance (Xrs) at 6 Hz was lower in obese than in control. In control, on changing to the supine posture, mean Rrs at 6 Hz rose to 2.9 $cmH_2O.l\text{-}1.s$, FRC fell by 0.68 liters, and Xrs at 6 Hz showed a small fall.	The total lung capacity in obese is lower than that of control. So, obesity can lead to post-operative hypoxia.
4.	Tyler IL et al.	$Sp0_2$, hypoxia, obesity	95	Hypoxemia occurred in 33 (35%) patients; severe hypoxemia occurred in 11 (12%). There was a statistically significant correlation (P less than 0.05) between hypoxemia and obesity.	Postoperative hypoxemia did not correlate significantly with an anesthetic agent, age, duration of anesthesia, or level of consciousness. Obesity was the only correlation.
5.	Joana Guimarães MD	$Sp0_2$, hypoxia, obesity	24	9% of patients in the Boussignac group and 50% in the Venturi group had a PaO_2 less than 60 mm Hg in at least 1 of the evaluations.	Application of Boussignac CPAP for 2 hours after extubation improved oxygenation but did not improve forced expiratory volume at 1 second and forced vital capacity.
6.	Delphine Van Hecke1	$Sp0_2$, hypoxia, obesity	100	Demographics were similar between groups. There was no difference in the incidence of hypoxemia during the first 2 postoperative days (control: 1.3%; intervention: 2.1%; $p = 0.264$).	The incidence of postoperative hypoxemia was not reduced by an open-lung approach with protective ventilation strategy in obese patients undergoing LBS. A pragmatic application of a PEEP level of 10 cm H_2O was comparable to individual PEEP titration in these patients.
7.	Haddon Pantel	$Sp0_2$, hypoxia, obesity	224	Baseline characteristics of the groups were similar. No significant differences in frequency of postoperative hypoxemia between the control and test groups were found at 6 (11.9%vs 10.4%; $P = .72$), 12 (5.4%vs 8.2%; $P = .40$), or 24 (3.7%vs 4.6%; $P = .73$) postoperative Hours.	Postoperative IS did not demonstrate any effect on postoperative hypoxemia, SaO_2 level, or postoperative pulmonary complications.
8.	Marcelo Gama de Abreu	$Sp0_2$, hypoxia, obesity	2013	The primary outcome occurred in 211 of 989 patients (21.3%) in the high level of PEEP group compared with 233 of 987 patients (23.6%) in the low level of PEEP group (difference, −2.3%[95%CI, −5.9%to 1.4%]; risk ratio, 0.93 [95%CI, 0.83 to 1.04]; $P = .23$). Among the 9 prespecified secondary outcomes, 6 were not significantly different between the high and low level of PEEP groups, and 3 were significantly different, including fewer patients with hypoxemia (5.0%in the high level of PEEP group vs 13.6% in the low level of PEEP group; difference, −8.6%[95%CI, −11.1% to 6.1%]; $P < .001$).	Among obese patients undergoing surgery under general anesthesia, an intraoperative mechanical ventilation strategy with a higher level of PEEP and alveolar recruitment maneuvers, compared with a strategy with a lower level of PEEP, did not reduce postoperative pulmonary complications.

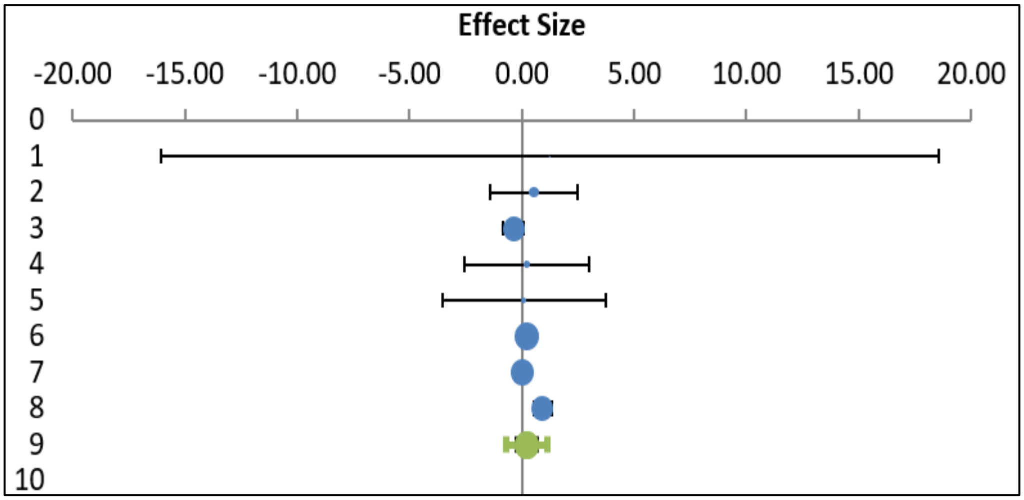

Figure 2: Forest Plot

Table 2: Effect size and percentages of weight of studies

#	Study name	Effect size	CI Lower limit	CI Upper limit	Weight
1	Pelosi P et al.	1.24	-16.07	18.56	0.05%
2	Sampson MG et al.	0.55	-1.42	2.51	4.08%
3	Yap JC et al.	-0.36	-0.81	0.09	21.39%
4	Tyler IL et al.	0.22	-2.53	2.97	1.76%
5	Joana Guimarães et al.	0.09	-3.55	3.73	1.12%
6	Delphine Van Heckel et al.	0.21	-0.01	0.44	26.22%
7	Haddon Pantel et al.	0.00	-0.32	0.32	23.92%
8	Marcelo et al.	0.92	0.52	1.33	21.46%

Table 3: Meta-data of studies included in the analysis

#	Study name	S average	Effect size	√n	Standard Error	n
1	Pelosi P et al.	37	1.243243243	4.472135955	8.273452	20
2	Sampson MG et al.	2.75	0.545454545	3.16227766	0.869626	10
3	Yap JC et al.	0.78	-0.358974359	3.741657387	0.208464	14
4	Tyler IL et al.	13.5	0.222222222	9.746794345	1.385071	95
5	Joana Guimarães et al.	8.62	0.092807425	4.898979486	1.75955	24
6	Delphine Van Heckel et al.	1.12	0.214285714	10	0.112	100
7	Haddon Pantel et al.	2.4	0	14.96662955	0.160357	224
8	Marcelo et al.	9.3	0.924731183	44.86646855	0.207282	2013

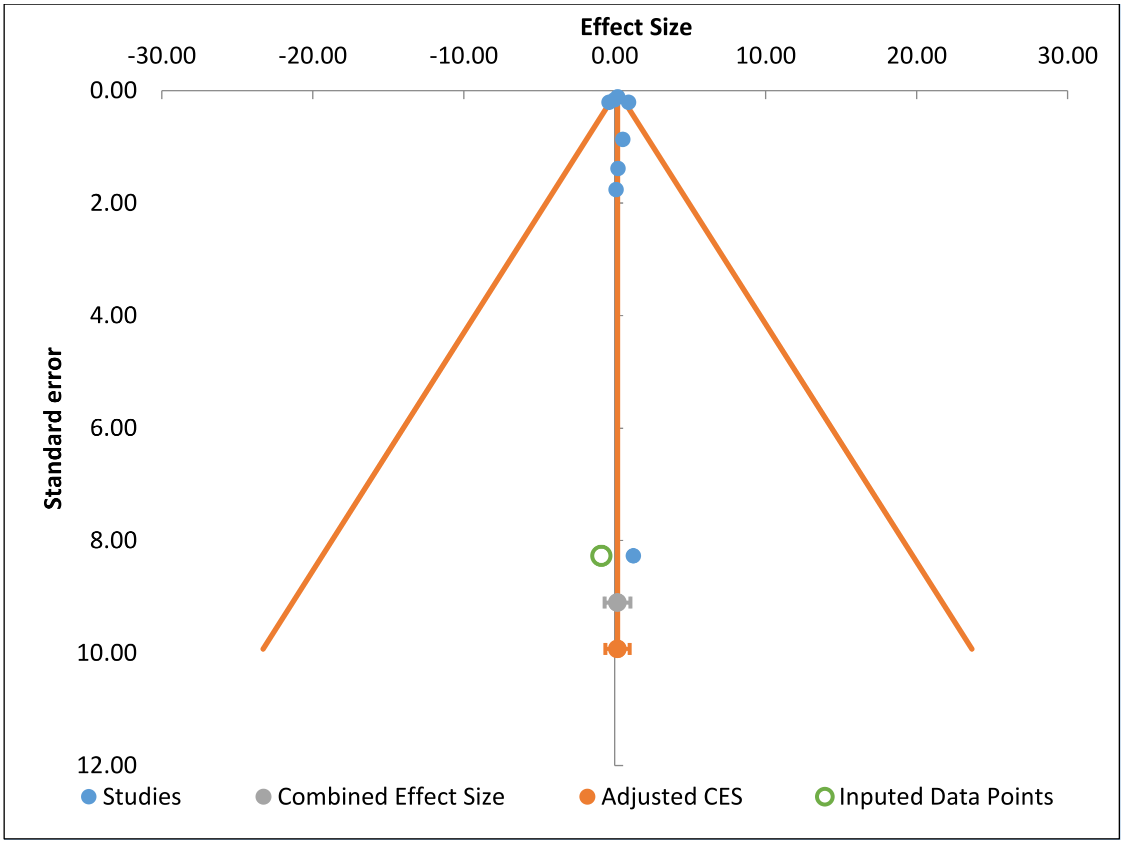

Figure 3: Publication Bias Analysis Funnel Plot with trim-and-fill

Table 4: Publication Bias Analysis Table showing heterogeneity, trim-and-fill.

Combined effect size	Observed		Heterogeneity	Adjusted
Effect Size	0.19		Q	21.15
SE	0.08		p_Q	0.007
CI Lower limit	0.00		I^2	62.18%
CI Upper limit	0.37		T^2	0.12
PI Lower limit	-0.67		T	0.34
PI Upper limit	1.04			
Combined effect size	**Adjusted**		**Trim and Fill**	**On**
Effect Size	0.19		Estimator for missing studies	Leftmost Run/Rightmost Run
SE	0.08		Search from mean	Left
CI Lower limit	0.01		Number of imputed studies	1
CI Upper limit	0.37			
PI Lower limit	-0.62			
PI Upper limit	0.99			

3.1. Meta-analysis of association with obesity

Association of obesity and postoperative hypoxia was compared among 8 studies. A total of 2500 subjects were included, 1265 subjects in the obese group, and 1235 subjects in the lean group. The heterogeneity test of the included data showed that the heterogeneity was moderate (I^2=62.18%), and considering the existence of clinical heterogeneity, the random effect model was adopted. The results of 5 out of the 8 studies show the effect size is less than of around 0.2 where the effect size of one of the studies is zero and one is close to 0.35 below zero. Another study shows a fairly moderate effect size of 0.54 while two of the studies showed a very high effect size of around 0.9 and above. (Table 3) The combined effect size is 0.19 which is insignificant. (Table 4)

3.2. Publication bias

The funnel plot of the studies is symmetrical and the possibility of publication bias is low. (Figure 3) Although the heterogeneity is high (Table 4), it might be due to other clinical factors interfering with results that probably need to be accounted for.

4. Discussion

This systematic review with meta-analysis aimed to analyze the association of post-operative hypoxia in patients with high body mass index as there are several studies done on this with contradicting results. Our purpose was to find studies that systematically collected data on patients post surgically, not only in the obese groups but also in the lean group which served as the control group. We aimed to compare the two groups and to observe any bio-statistically significant co-relationship between the obesity and hypoxia.

Obesity is often related to a number of other diseases and thus can lead to observation bias. Specifically studies collecting data incorrectly might have selection bias. However, our results collected show that the risk of bias is moderate if not minimal. The data extracted from the studies were analyzed with a funnel-plot (Figure 3) which seems to be quite symmetrical. And the heterogeneity can be seen in (Table 4). Which is also quite moderate given that this is clinical data and there are so many factors that can affect the outcome.

Comparing the data of the lean group with the obese group from the studies we observed an insignificant positive effect and the results lean more towards the null hypothesis. This could be because the healthcare staff were taking extra care for the obese patients. Since doctors and anesthesiologists generally are extra careful with obese patients, they might be giving them higher levels of oxygen, for longer durations to prevent hypoxia. However, these studies have not mentioned this aspect.

One reason this could be the case is the differences in the body masses of the patients and the kinds of anesthetic agents used. Insignificant difference can be a result of these factors or post-surgical hypoxia might not have a significant enough association to produce positive results on its own and might be dependent on the existence of co-existing conditions that would result in hypoxia in the post anesthesia care unit or intensive care unit.

5. Limitations and practical applications

We acknowledge several limitations to this meta-analysis, some of which are related to the available studies on the topic, the limitations of differences in the methods of collecting the data, the differences of the instruments used, the types of patients undergoing different kinds of surgeries and the relatively different number of patients included in the studies. However, the results of the studies are still quite consistent and the combined effect size is 0.19 which shows that the way obese patients are being treated could be improved by compensating the obese patients by supplementing with more oxygen and increase monitoring of blood oxygen levels.

Finally, it is important to note that it is not only obesity that can lead to hypoxia but there are also several other risk factors such as decreased functional residual capacity, increased total respiratory resistance, diminished thoraco-pulmonary compliance and these factors should also be taken into account when dealing with obese patients.

6. Conclusion

In conclusion, the results obtained through our study prove that the obesity has no significant association with postoperative hypoxia in surgical patients.

7. Conflict of interest

No conflict of interest was declared by the authors.

8. Authors' contribution

YT: Concept, research, writing the article

MSM: Data collection, analysis, grammar correction

LB: Corresponding author

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