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ORIGINAL CONTRIBUTIONS

Improvement in Nocturnal Hypoxemia in Obese Patients with Obstructive Sleep Apnea after Bariatric Surgery: a Meta-Analysis

Yuxiang Zhang [1] · Wenyue Wang [1] · Chengcan Yang [1] · Jiahui Shen [1] · Meilong Shi [1] · Bing Wang [1]

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Abstract

Objective To conduct a meta-analysis examining the effects of bariatric surgery on nocturnal hypoxemia in obese patients with obstructive sleep apnea (OSA).

Methods PubMed, EMBASE, Cochrane Library, and Web of Science were searched (the last search date was June 10, 2018) to identify relevant clinical studies. The mean arterial oxygen saturation ($MeanSaO_2$), nadir oxygen saturation ($NadirSaO_2$), apnea hypopnea index (AHI), and body mass index (BMI) data during the perioperative period were extracted and analyzed using a random effects model. Then, we performed subgroup and sensitivity analyses and calculated the publication bias to assess the between-study heterogeneity.

Results In total, 15 studies with 636 patients were included; 13 were prospective observational trials, 1 was a randomized controlled trial (RCT), and 1 was a retrospective trial. After surgery, the $MeanSaO_2$ and $NadirSaO_2$ increased by 1.36 [95% CI (0.72, 2.00)] and 1.08 [95% CI (0.68, 1.49)], respectively, and the AHI and BMI decreased by 1.11 [95% CI (0.82, 1.40)] and 1.97 [95% CI (1.67, 2.27)], respectively. However, the heterogeneity across all trials was high; we identified some of the sources of that heterogeneity through subsequent subgroup and sensitivity analyses.

Conclusions Bariatric surgery is effective at improving nocturnal hypoxemia in obese patients with OSA; it also reduces body weight and the number of apnea events. More randomized controlled and comparative trials are necessary in the future to confirm our findings and to explore the potential underlying mechanisms.

Keywords Meta-analysis · Bariatric surgery · Obstructive sleep apnea · Nocturnal hypoxemia · Apnea hypopnea index

Yuxiang Zhang and Wenyue Wang contributed equally to this work.

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✉ Bing Wang
pingwing@126.com

Yuxiang Zhang
zyx447255507@163.com

Wenyue Wang
wangwenyue@sjtu.edu.cn

Chengcan Yang
magicycc@163.com

Jiahui Shen
13120509531@163.com

Meilong Shi
764250772@qq.com

[1] Department of General Surgery, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, 639 Zhi Zao Ju Road, Shanghai 200011, China

Introduction

The prevalence of obesity is increasing worldwide and has imposed large medical and economic burdens on our society [1]. Obesity is an important risk factor for the development of several comorbidities including obstructive sleep apnea (OSA) [2, 3], and the risk of developing OSA increases 1.14-fold [95% CI (1.10, 1.19)] for every unit increase in body mass index (BMI) [2, 3]. OSA is characterized by repeated apnea, sleep interruption, and hypoxemia during sleep, which may be complicated by, among other problems, hypertension, cardiovascular disease, stroke, and decreased cognitive function [2, 4, 5]. Bariatric surgery is currently recognized as an effective treatment for morbid obesity and its complications [6, 7]. Studies have shown that the rate of improvement in obesity in patients with OSA after bariatric surgery is 68 to 84% [8, 9]. However, there has been no agreement until now regarding whether weight-loss surgery can effectively correct hypoxemia. Therefore, the aim of this study was to conduct a systematic review and meta-analysis of the literature regarding the efficacy of bariatric surgery with regard to blood oxygen levels in obese patients with OSA.

Methods

Search Strategy

Studies were identified by searching the PubMed, EMBASE, Cochrane Library, and Web of Science databases with the keywords ("bariatric surgery" OR "metabolic surgery" OR "weight loss surgery" OR "obesity surgery" OR "diabetes surgery" OR "gastric bypass" OR "Roux-en-Y gastric bypass" OR "sleeve gastrectomy" OR "gastric band" OR "gastric banding" OR "biliopancreatic diversion" OR "duodenal switch" OR "duodenojejunal bypass") AND ("obstructive sleep apnea" OR "upper airway resistance sleep apnea syndrome" OR "obstructive sleep apnea syndrome" OR "obstructive sleep apnea hypopnea syndrome" OR "obstructive sleep apnea") AND ("obese" OR "obesity" OR "overweight"). Two independent investigators reviewed all identified articles based on the following selection and inclusion criteria: (a) all obese OSA patients underwent bariatric surgery after adequate preoperative evaluation, and (b) all obese OSA patients received polysomnography tests at baseline and after surgery, with the relevant parameters reported in the full-text articles (including, at a minimum, mean arterial oxygen saturation (MeanSaO_2) or nadir oxygen saturation (NadirSaO_2)). Studies with the following conditions were excluded: (a) the study did not report the outcomes of interest or the data could not be effectively extracted, (b) the study involved nonhuman subjects, or (c) the full text of the article could not be found. Disagreements between reviewers were resolved by discussion or consensus with a third reviewer. The last search date was June 10, 2018, and the language was restricted to English. A flow chart of the search process is outlined in Fig. 1.

Data Extraction and Analysis

The data extracted and summarized from the studies consisted of the first author's name, publication year, country, study design, surgical procedure, sample size, follow-up time, participant characteristics, and measured outcomes (i.e., MeanSaO_2, NadirSaO_2, apnea hypopnea index (AHI), and BMI) at baseline and after surgery.

This meta-analysis followed the recommendations of the Cochrane Collaboration and conformed to both the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Data analysis was performed using STATA v.12 statistical analysis software. For

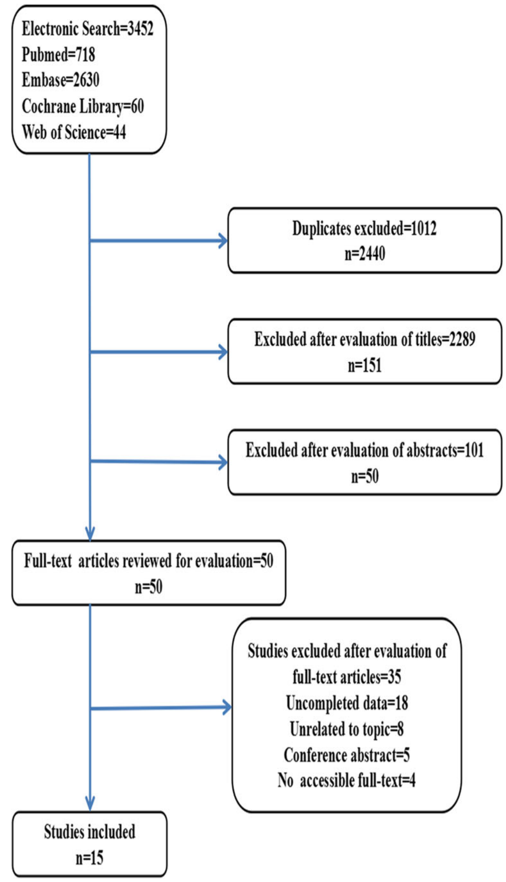

Fig. 1 Flow chart of the literature search process

continuous variables, the standardized mean difference (SMD) was selected to constitute the combined effect value, and the 95% confidence interval (CI) was calculated as part of the statistical description. If the 95% CI did not include zero, then the point estimate for the combined effect value was considered statistically significant when $p < 0.05$.

Heterogeneity Assessments

The I^2 statistic was calculated to determine the heterogeneity. At $I^2 > 50\%$ and $p < 0.1$, the heterogeneity was considered to be statistically significant across the studies. If significant heterogeneity was identified, we used the random effects model to combine the effect sizes; otherwise, the fixed effects model was used.

A variety of methods were used to explore the sources of heterogeneity. First, a subgroup analysis was conducted. The included studies were divided into a laparoscopic adjustable gastric banding (LAGB) group, a Roux-en-Y gastric bypass (RYGB) group, and a sleeve gastrectomy (SG) group to investigate the impact of the surgical approach on heterogeneity. Second, a sensitivity analysis was performed to evaluate the stability of the combined effect value and the source of the heterogeneity via the trim-and-fill method and the leave-one-study-out method. Third, publication bias was evaluated with Egger's test to quantitatively analyze the publication bias.

Results

In total, 3452 results were retrieved by the search. After deduplicating and reviewing the titles, 3301 unrelated publications were excluded; then, after reviewing the abstracts and full-text articles, 136 publications that did not meet the inclusion and exclusion criteria were removed. Hence, the remaining 15 articles with a total of 636 patients were incorporated into the final meta-analysis. These studies consisted of 13 prospective observational trials [8, 10–21], 1 RCT [22], and 1 retrospective trial [23]. The characteristics of all included studies are shown in Table.1.

Improvement in the Severity of OSA: a Meta-Analysis of $MeanSaO_2$, $NadirSaO_2$ and AHI

Complete data were reported by 11 studies for $MeanSaO_2$ [8, 10, 11, 13–17, 20, 22, 23], 12 studies for $NadirSaO_2$ [11–22], and 13 studies for AHI [8, 11–22]. The results showed that nocturnal hypoxemia was significantly improved in obese patients with OSA. The $MeanSaO_2$ [SMD 1.36, 95% CI (0.72, 2.00), $p < 0.001$], $NadirSaO_2$ [SMD 1.08, 95% CI (0.68, 1.49), $p < 0.001$], and AHI [SMD -1.11, 95% CI (− 1.40, 0.82), $p < 0.001$] were all significantly different between the preoperative and postoperative periods. In other words, the $MeanSaO_2$ and $NadirSaO_2$ increased by 1.36 [95% CI (0.72, 2.00)] at mean 12.5 months and 1.08 [95% CI (0.68, 1.49)] at mean 10.1 months, respectively. However, there was fairly high between-study heterogeneity for the measured outcomes ($MeanSaO_2$ $I^2 = 94.2\%$, $p < 0.001$, $NadirSaO_2$ $I^2 = 82.5\%$, $p < 0.001$, AHI $I^2 = 73.8\%$, $p < 0.001$) (Fig. 2, Sfig.1).

The subgroup analysis was conducted based on the surgical approach. We again found that nocturnal hypoxemia in obese OSA patients improved markedly after surgery. The between-study heterogeneity for $MeanSaO_2$, $NadirSaO_2$, and AHI all disappeared in the LAGB group ($MeanSaO_2$ $I^2 = 0$, $p = 0.608$; $NadirSaO_2$ $I^2 = 0$, $p = 0.460$; AHI $I^2 = 0$, $p = 0.708$). In the RYGB group, the heterogeneity decreased to 5.2% ($p = 0.384$) for AHI but was still high for $MeanSaO_2$ ($I^2 = 96.4\%$, $p < 0.001$) and $NadirSaO_2$ ($I^2 = 88.6\%$, $p < 0.001$), which may be associated with the early publication date of three studies, when the surgical methods were still immature [10, 11, 23], and the differences in the characteristics of the participants at baseline (Table 2; Figs.3 and 4, Sfig. 2). In addition, the heterogeneity for $MeanSaO_2$ disappeared as well in the SG group ($MeanSaO_2$ I2 = 0, $p = 0.737$). Overall, we concluded that the surgical method may also be a source of heterogeneity.

The internal differences were eliminated using the trim-and-fill method after several cycles, indicating that the conclusion is fairly stable (Sfigs. 3 and 4). Next, through the

Table 1 Description of the included studies

Author	Year	Country	Study type	Sample size	Follow-up (months)	Operation type	BMI (kg/m^2)		AHI		$MeanSaO_2$(%)		$NadirSaO_2$(%)	
							Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Guardiano	2003	USA	Retrospective	8	28 ± 20	RYGB	NS	NS	NS	NS	95	97	74	87
Haines	2007	USA	Prospective	101	11(6–42)	RYGB	56	38	NS	NS	77	86	NS	NS
Fritscher	2007	Canada	Prospective	12	24	RYGB	55.5	34.1	46.5	16	85.7	94.5	64.7	78.8
Lettieri	2008	USA	Prospective	24	12	LAGB	51	32.1	47.9	24.5	NS	NS	76.5	84.5
Krieger	2012	USA	Prospective	20	12	LAGB	47.18	35.62	34.2	19	95.15	95.39	80.58	84
Fredheim	2013	Norway	Prospective	71	12	RYGB	47.5	33.5	29.3	7.7	92.8	95.1	75.8	95.1
Aguiar	2014	Brazil	RCT	16	3	LAGB	48.15	36.91	15.65	6.26	93.3	94.3	83,25	85
Bae E.K.	2014	Korea	Prospective	10	13.9	RYGB	39.9	26.9	51	9.3	93.5	95.8	81.8	86
Ravesloot	2014	Netherlands	Prospective	110	7.7	LAGB, RYGB, SG	45.4	36.3	39.5	15.6	92.2	94.4	75.1	84
Jianyin Zou	2015	China	Prospective	44	6	RYGB	31.1	24.4	22.4	7.1	93.4	95.5	77.1	86.7
Xiao Jiao	2016	China	Prospective	39	6–12	RYGB	30.73	24.24	13	3	NS	NS	82	89
Shaarawy	2016	Egypt	Prospective	22	12	SG	48.2	35.9	55.8	12.8	NS	NS	67.2	92.2
Suliman	2016	Egypt	Prospective	20	8.25 ± 0.96	SG	60.51	41.49	18	10	92.86	95	82.35	87.1
Raouf Amin	2017	USA	Prospective	7	1	RYGB, SG	NS	NS	13	4.5	NS	NS	84	89
Peromaa	2017	Finland	Prospective	132	12	RYGB	43.9	33	27.6	9.9	92	93.3	NS	NS

RYGB Roux-en-Y gastric bypass, *LAGB* laparoscopic adjustable gastric banding, *SG* sleeve gastrectomy, *NS* not specified

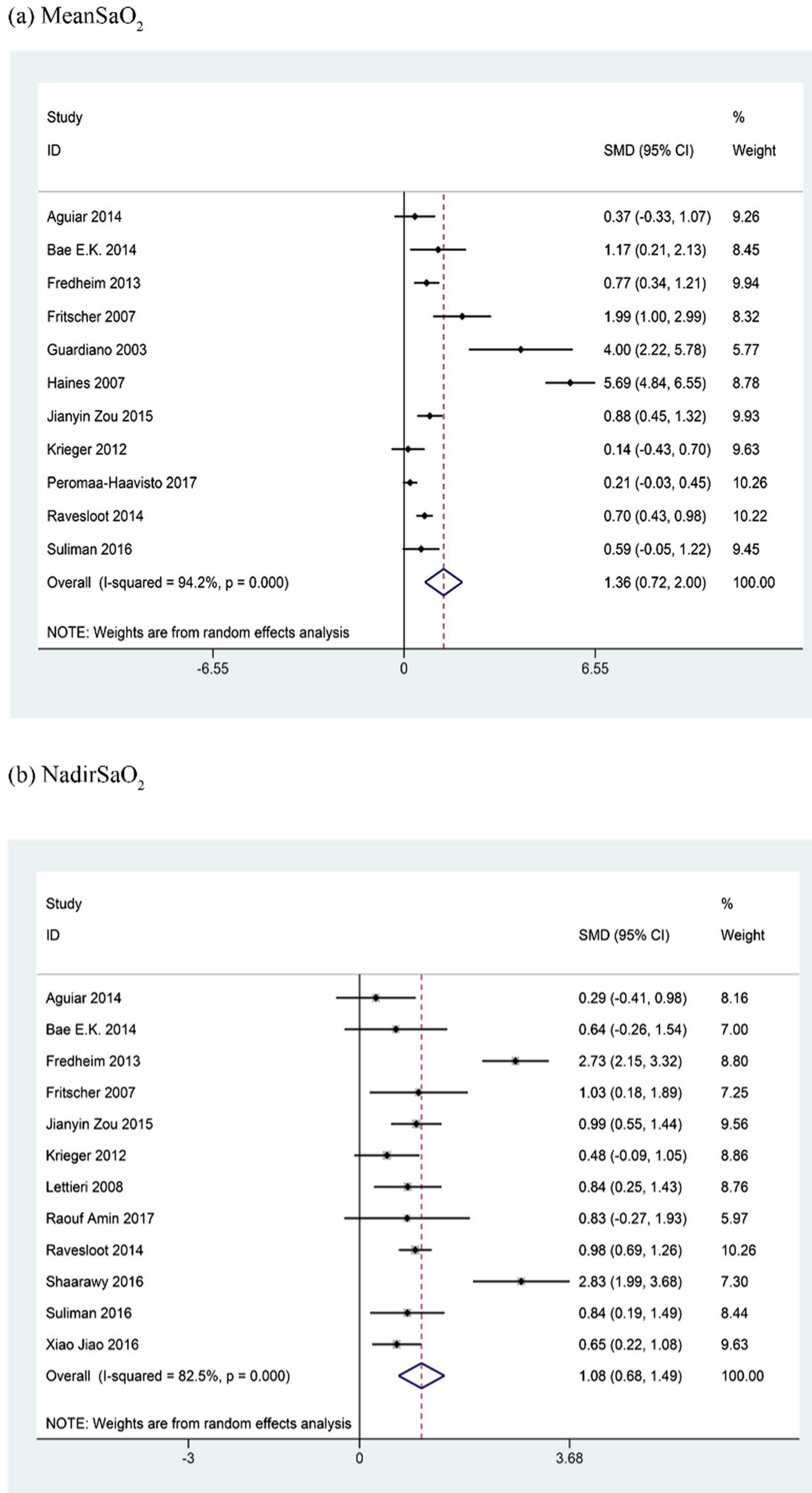

Fig. 2 Forest plots for $MeanSaO_2$ (a) and $NadirSaO_2$ (b) at baseline and after surgery

leave-one-study-out method, we found that the between-heterogeneity for $MeanSaO_2$ decreased significantly from 94.2 to 76.6% ($p < 0.001$) after excluding one study [10] and that of $NadirSaO_2$ disappeared ($I^2 = 0$, $p = 0.705$) after excluding an additional two studies [19, 24], indicating that these studies may be the sources of the heterogeneity. After carefully reviewing the full-text articles, we found that the OSA patients included in these trials tended to have more severe hypoxemia at baseline, generally received continuous positive airway pressure (CPAP) therapy after surgery, and had longer

Table 2 Subgroup analysis

Subgroup	Stratification	NO. of studies	P value for heterogeneity	I^2(%)	Pooled standardized mean differences	P value for heterogeneity between groups
$MeanSaO_2$						
Surgery	LAGB	2	0.608	0	0.23 (− 0.21, 0.67)	0.069
Type	RYGB	7	< 0.001	96.4	0.79 (0.61, 0.97)	0.069
	SG	2	0.737	0	0.69 (0.43, 0.94)	0.069
	OVERALL	11	< 0.001	94.2	0.70 (0.56, 0.84)	
$NadirSaO_2$						
Surgery	LAGB	3	0.460	0	0.56 (0.21, 0.91)	0.016
Type	RYGB	5	< 0.001	88.6	1.17 (0.92, 1.42)	0.016
	SG	4	< 0.001	83	1.10 (0.86, 1.35)	0.016
	OVERALL	12	< 0.001	82.5	1.02 (0.87, 1.18)	
AHI						
Surgery	LAGB	3	0.708	0	− 0.71 (− 1.07, − 0.35)	0.094
Type	RYGB	6	0.384	5.2	− 0.92 (− 1.09, − 0.75)	0.094
	SG	4	< 0.001	91.5	− 1.16 (− 1.41, − 0.92)	0.094
	OVERALL	13	< 0.001	73.8	− 0.96 (− 1.09, − 0.83)	
BMI						
Surgery	LAGB	3	0.080	60.5	− 1.59 (− 2.00, − 1.19)	0.002
Type	RYGB	6	0.071	50.7	− 2.10 (− 2.30, − 1.89)	0.002
	SG	3	0.023	73.6	− 1.54 (− 1.80, − 1.28)	0.002
	OVERALL	12	< 0.001	68.9	− 1.84 (− 1.99, − 1.69)	

LAGB laparoscopic adjustable gastric banding, *RYGB* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *AHI* apnea hypopnea index, *BMI* body mass index

follow-up periods, all of which resulted in marked increases in the postoperative $MeanSaO_2$ and $NadirSaO_2$ (Sfig. 5). In summary, we concluded that the differences among the participants included in the present study may have influenced the results.

Finally, the result of Egger's test showed that the *p* value was greater than 0.05, and each study was evenly distributed on both sides of the line in the forest plot, indicating that there was little or no publication bias across the included studies and that publication bias was not a source of heterogeneity (Fig. 5, Sfig. 8).

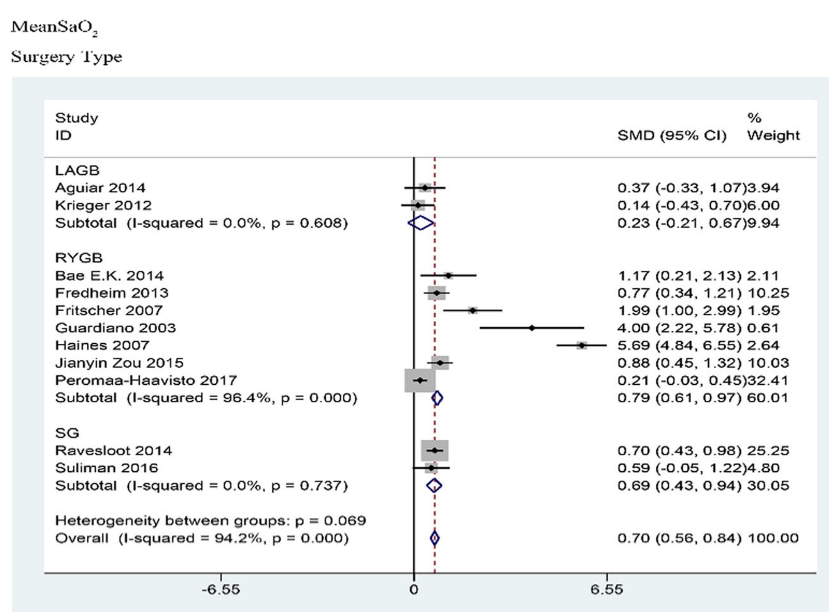

Fig. 3 Subgroup analyses of $MeanSaO_2$

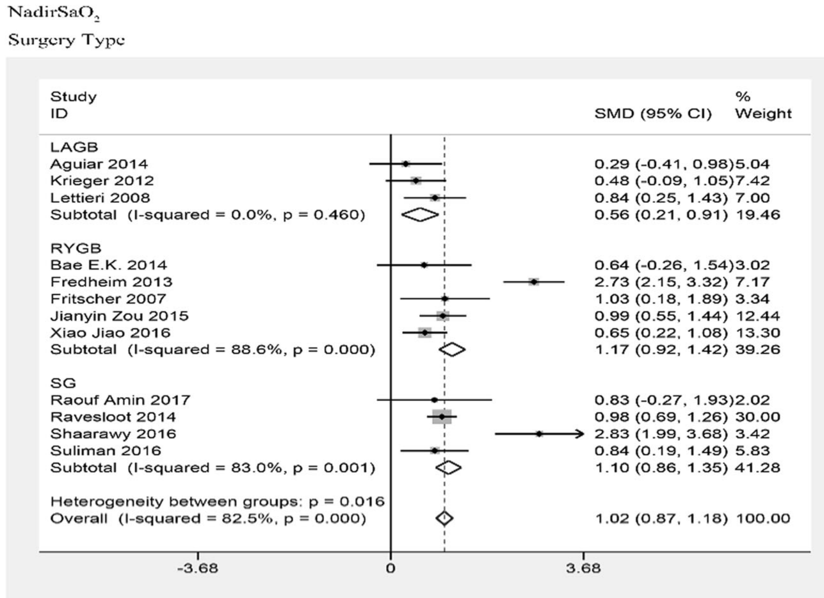

Fig. 4 Subgroup analyses of $NadirSaO_2$

Improvement in the Severity of Obesity: a Meta-Analysis of BMI

In total, 12 studies reported complete data for BMI [8, 11–20, 22]. The data showed that bariatric surgery resulted in significant weight loss [SMD − 1.97, 95% CI (− 2.27, − 1.67), $p < 0.001$]. However, there was fairly high heterogeneity across the trials for the measured outcomes (BMI I^2 = 68.9%, $p < 0.001$) (Sfig. 1).

A subgroup analysis was performed based on the surgical approach. We found that obese patients with OSA all lost significant amounts of weight after all types of surgeries. The between-heterogeneity values for BMI were reduced in all three groups but were still high (LAGB I^2 = 60.5%, $p = 0.080$; RYGB I^2 = 50.7%, $p = 0.071$; SG I^2 = 73.6%, $p = 0.023$), demonstrating that different surgical approaches may be a source of heterogeneity and that the surgeries included in the SG group still need to be investigated (Table 2; Sfig. 6).

The internal differences were eliminated with the trim-and-fill method after several cycles, indicating that the conclusion is fairly stable (Sfig. 4). Next, the leave-one-study-out method did not significantly alter the pooled results (Sfig. 7). In summary, bariatric surgery was effective at inducing weight loss and usually resulted in improvements in OSA.

Finally, the results of Egger's test showed that the p value was greater than 0.05, and each study was evenly distributed on either side of the line in the forest plot, indicating that there was little or no publication bias across the included studies and that publication bias was not a source of heterogeneity (Sfig. 8).

Discussion

There is longitudinal data indicating that the estimated prevalence of OSA has increased substantially over the last two decades [25]. CPAP therapy is currently recognized as a routine treatment for OSA. However, studies have reported that CPAP compliance is relatively poor and that nearly half the patients discontinue therapy after 3 months [26, 27]. Fortunately, bariatric surgery has been recommended as a treatment for OSA patients with a BMI > 30 kg/m^2, and consensus guidelines for the perioperative management of OSA patients undergoing bariatric surgery have been developed [28]. In the present meta-analysis, the results showed that the $MeanSaO_2$ and $NadirSaO_2$ increased by 1.36 [95% CI (0.72, 2.00)] at mean 12.5 months and 1.08 [95% CI (0.68, 1.49)] at mean 10.1 months, respectively, indicating that bariatric surgery was effective at improving the severity of OSA in obese patients, particularly in terms of their nocturnal hypoxemia status.

Even though AHI is the gold standard for diagnosing OSA, it is not a comprehensive indicator of the severity of this disease. (reviewer #2). Intermittent hypoxia plays a key role in the development of cardiovascular complications in patients with OSA by inducing the production of reactive oxygen species, resulting in oxidative stress and inflammation [29]. However, until the present study, no meta-analysis had been conducted to evaluate the changes in arterial oxygen levels after surgery in obese OSA patients. Therefore, in this study, the $MeanSaO_2$ and $NadirSaO_2$ derived from polysomnographs were incorporated into the measured outcomes along with the changes in AHI and BMI to assess the

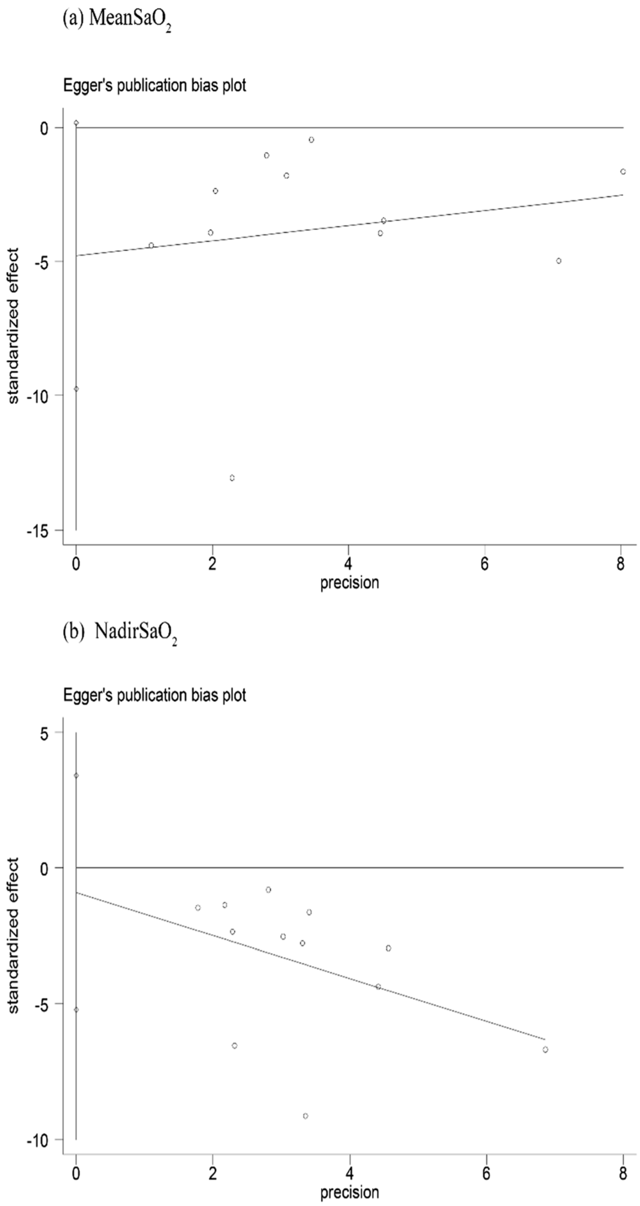

Fig. 5 Egger's test of MeanSaO_2 (**a**) and NadirSaO_2 (**b**)

effects of bariatric surgery on nocturnal hypoxemia in obese patients with OSA.

Already recognized as one of the most effective therapies for obesity and related metabolic diseases, bariatric surgery can also improve nocturnal hypoxemia in obese OSA patients. The potential mechanisms by which weight-loss surgery improves nocturnal hypoxemia may involve redistributing neck fat, restoring muscle tissue, and altering the upper airway structure, thereby improving apnea and hypoxemia [30]. Even though, we must adequately balance the risks and benefits of bariatric surgery when choosing it as a treatment for morbid obesity.

This study had several limitations. First, 15 studies with 636 patients were recruited in the present meta-analysis, but there was only 1 RCT [22], and most of the studies, both prospective and retrospective, were single-armed studies, which resulted in the identification of only two high-quality studies [14, 22]. Second, our results showed statistically significant heterogeneity, which can be attributed to a variety of possible confounding factors including the demographics, sample sizes, follow-up times, and publication years, as well as recent advances in surgical technology and sleep-breathing monitoring devices. Thus, we then performed sensitivity and subgroup analyses to explore the sources of heterogeneity. Third, we excluded many excellent studies because the data were incomplete, restricting the representation of the target population. Overall, studies with large sample sizes and long-term RCTs are needed in the future.

Conclusions

In conclusion, this meta-analysis demonstrated that bariatric surgery is effective at improving nocturnal hypoxemia in obese OSA patients and induces significant weight loss, which may be related to the positive cardiovascular outcomes that have been reported recently. Although there existed relatively high between-study heterogeneity, we performed several analyses to investigate the sources and verify our findings. Future studies should address the lack of RCTs and comparative trials; in the future, these studies should consider postintervention periods, response curves, and the underlying mechanisms that result in the resolution of OSA, which would help us clinically manage this disease more successfully.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that there are no conflicts of interest.

Ethical Approval For this type of study, formal consent is not required.

Financial Disclosure None.

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