



Review

Outcomes after laparoscopic anti-reflux surgery related to obesity: A systematic review and meta-analysis



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ABSTRACT

Background: Laparoscopic Anti-Reflux Surgery (LARS) is an established alternative treatment to pharmacological therapy for patients with Gastro Oesophageal Reflux Disease (GORD), yet its safety and efficacy in obese patients is controversial. A systematic review and meta-analysis was performed to compare LARS related to obesity.

Methods: Embase, MEDLINE and the Cochrane Library (January 1970 to July 2017) were searched for studies reporting clinical outcomes of LARS in patient cohorts stratified by Body Mass Index (BMI). Data was grouped according to BMI, < 30 kg/m² (non-obese) and ≥ 30 kg/m² (obese). Primary outcome measures were reflux recurrence, operative morbidity, re-intervention (redo surgery and endoscopic dilatation), conversion to open surgery, and early return to theatre. Results were pooled in meta-analyses as Odds Ratios (OR).

Results: Thirteen eligible observational studies comparing LARS in non-obese (n = 6246) and obese (n = 1753) patients were identified. Recurrence of reflux was significantly lower in the non-obese cohort (OR 0.28, 95% C.I. 0.13 to 0.61, p = 0.001), however no significant differences were observed in rates of operative morbidity (OR 0.82, 0.54 to 1.23, p = 0.33), redo surgery (OR 0.94, 0.51 to 1.72, p = 0.84), endoscopic dilatation (OR 0.98, 0.45 to 2.17, p = 0.97), conversion to open surgery (OR 0.96, 0.50 to 1.85, P = 0.90), or early return to theatre (OR 0.77, 0.43 to 1.38, p = 0.39).

Conclusions: LARS can be performed safely in obese patients, but risks higher GORD recurrence. Clinicians and patients should be aware that obesity may adversely affect LARS outcome and careful consideration be given in the consent process inherent within the optimal management of GORD.

1. Introduction

Gastro oesophageal reflux disease (GORD) is among the commonest contemporary problems faced by medical practitioners. Precise details regarding its prevalence are unclear, but there remains a perception that it is rising, with reports commonly citing some 10–30% of the population in the western world [1]. The condition was first described in 1935 by the American gastroenterologist, Asher Winkelstein, although the classic symptoms were described earlier in 1925 [2,3].

Obesity in the West represents a contemporaneous increasing health concern. Data published as a part of the World Health Organization (WHO) study in 2014, indicated that 26% of adults in the United Kingdom were clinically obese with a Body Mass Index (BMI) greater than 30 kg/m² [2] [4]. Moreover, the worldwide prevalence has more than doubled between the years 1980–2014 [4]. Any reasonable

observer might therefore expect GORD and obesity to be related, and indeed pathophysiological theories for an association exist and include, increased intra-abdominal pressure, diminished lower oesophageal sphincter pressure, and reduced gastric motility, resulting in symptomatic GORD being up to three times more prevalent in obese patients [5–12].

Laparoscopic Anti-Reflux Surgery (LARS) has become an established alternative to lifelong pharmacological acid suppression, and in patients refractory to such therapy. A variety of fundoplication procedures, in which the stomach is used to reinforce a dysfunctional lower oesophageal sphincter at the gastro-oesophageal junction, have been shown to be both safe and effective, with the Nissen fundoplication reportedly the commonest performed [13–16]. LARS in obese patients however, has been a source of controversy in recent years, with experts citing poorer clinical outcomes in this patient cohort, not least because

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of the associated technical difficulties and the increased postoperative intra-abdominal pressure allegedly putting strain on the diaphragmatic hiatus. Certainly, the literature is conflicting, with no consensus regarding relative complication rates, recurrence of reflux, or para-oesophageal herniation. Given these controversies some surgeons have questioned the merits of LARS for GORD in the obese, and the aim of this study was to perform a systematic review and meta-analysis to compare the clinical outcomes of LARS related to obesity. The primary outcome measure was the relative incidence of recurrent reflux related to BMI. Secondary outcome measures were relative incidence of perioperative complications, re-intervention rates in the form of endoscopic dilatation or surgery, conversion to open surgery, and early return to theatre.

2. Materials and methods

2.1. Literature search strategy

A systematic review of the literature was carried out according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) [17]. Embase, MEDLINE, and the Cochrane Library databases were systematically searched from January 1970 to July 2017 for studies reporting clinical outcomes of laparoscopic anti-reflux surgery (LARS) in patient cohorts stratified by Body Mass Index (BMI). The following terms were used to identify studies: fundoplication, Nissen, Rossetti, Toupet, Lind, Guarner, Dor, Thal, reflux, obese, obesity, weight, BMI. Reference lists of retrieved articles were used to hand search and identify further potentially relevant articles.

2.2. Data extraction

A standardized protocol was used for all data extraction by two authors (TA, AL) and discussion amongst all authors was used to reach agreement regarding discrepancies encountered. The following information was obtained from each study: first author, year of publication, study design, number of subjects undergoing LARS stratified by BMI, perioperative complications, conversion to open surgery, early return to theatre, need for redo surgery or endoscopic dilatation, recurrence of reflux symptoms, and mean follow up.

All included studies stratified patients into cohorts according to the recognized WHO BMI classification. Data from all of these studies were extracted and re-organised into two broader categories for the purpose of meta-analyses: non-obese (BMI < 30) versus obese (BMI ≥ 30).

2.3. Inclusion and exclusion criteria

Studies comparing outcomes of LARS related to patients' BMIs were included. Studies that did not report outcomes, experimental studies, case reports and unpublished data from conference abstracts were excluded. Studies not stratifying patients using the WHO BMI classification were excluded.

2.4. Outcomes of interest

Outcome measures examined included post-operative recurrence of reflux, perioperative complications, need for re-intervention by redo surgery and endoscopic dilatation, rates of conversion from laparoscopic to open surgery, and return to theatre during the index admission.

Reflux recurrence was measured either subjectively, through the reporting of clinical symptoms, or objectively utilizing methods such as 24-h pH studies, oesophageal manometry, barium swallow and gastroscopy. A number of studies used both subjective and objective measures to define recurrence. Publications that reported reflux using various validated scoring systems were excluded as meta-analysis of this data was not possible.

2.5. Statistical analysis

The meta-analysis was performed in accordance with the Cochrane Collaboration and PRISMA guidelines using Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) Dichotomous variables were analysed using Odds Ratio (OR). Due to the anticipated heterogeneity of the data, a Mantel–Haenszel random-effects model was used during statistical analysis of all meta-analyses. The pooled ORs were reported with 95% confidence intervals (CI). The point estimate where OR was considered statistically significant was $p < 0.05$ and where the 95% CI did not span 1. The Newcastle-Ottawa Scale was used to evaluate the quality of non-randomized cohort studies [18]. This examines studies using three domains, assessing the methodology of patient selection, comparability of cohorts, and finally outcome assessment and follow up. A star scoring system correlates with study quality. At least seven stars from a maximum of nine were deemed to indicate a high-quality study.

2.6. Heterogeneity and publication bias

The I^2 value was used to assess heterogeneity, quoted for each meta-analysis. Publication bias was assessed using Funnel Plots, with asymmetry implying either recall or publication bias [19].

3. Results

The full texts of 35 publications were obtained; 13 of these were cohort studies that met criteria for review (Fig. 1). Statistical analysis was carried out on 7999 patients who had undergone therapeutic laparoscopic anti-reflux surgery, of whom 6246 patients were non-obese and 1753 patients obese.

3.1. Characteristics of included studies

Six of the included studies were retrospective cohort studies [20–25] and seven were prospective cohort studies [26–32]. Table 1 summarizes the study characteristics. Six studies that investigated recurrence of reflux symptoms following LARS were included in the meta-analysis [20,22,24–26,29]. Eight studies explored perioperative complications [21–23,26–28,30,31], eight studies reported on the need for

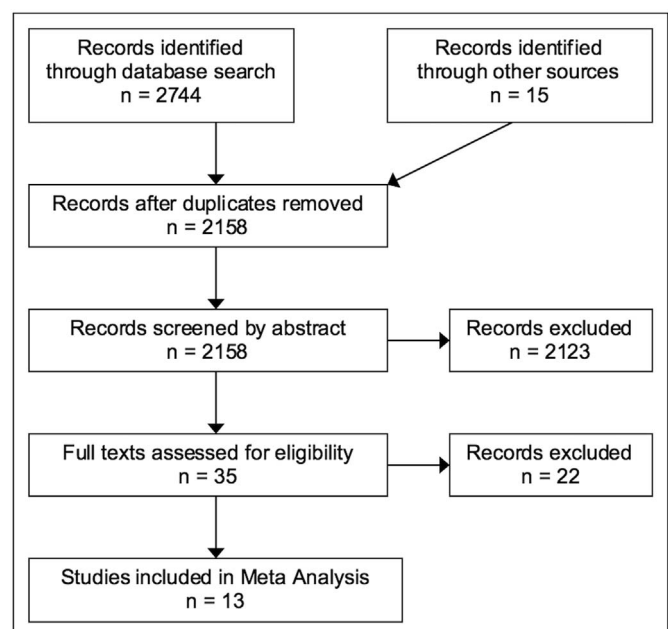


Fig. 1. Identification of eligible studies.

Table 1
Characteristics of studies included in the meta-analyses.

First author	Year published	Study design	Total n =	Follow up (months)	Study BMI categories	BMI regrouping for meta-analyses	BMI n =	Reported outcomes included in meta analyses	Study quality score
Tsuboi [20]	2009	Retrospective cohort	145	77	< 25, 25–29.9, ≥ 30	< 30 ≥ 30	135 10	RR	9
Telem [21]	2014	Retrospective cohort	4231	1	< 35, ≥ 35	< 35 ≥ 35	3496 735	PC, ERT	7
Tekin [26]	2011	Prospective cohort	1000	53	< 25, 25–29.9, ≥ 30	< 30 ≥ 30	868 132	RR, PC, RE-HS, RE-ED, CON	7
Fraser [27]	2001	Prospective cohort	194	38.4	< 25, 25–29.9, ≥ 30	< 30 ≥ 30	128 66	PC, RE-HS, CON	8
Ng [28]	2007	Prospective cohort	366	12	< 30, ≥ 30	< 30 ≥ 30	292 74	PC, RE-HS, RE-ED, CON, ERT,	7
Perez [29]	2001	Prospective cohort	224	37	< 25, 25–29.9, ≥ 30	< 30 ≥ 30	176 48	RR	8
Winslow [30]	2003	Prospective cohort	504	35	< 25, 25–29.9, ≥ 30	< 30 ≥ 30	292 212	PC, RE-HS, RE-ED, ERT	7
D'Alessio [31]	2005	Prospective cohort	257	26	< 25, 25–29.9, ≥ 30	< 30 ≥ 30	195 62	PC, ERT, OD	8
Anvari [22]	2005	Retrospective cohort	140	41.6	< 30, ≥ 35	< 30 ≥ 35	70 70	RR, PC, RE-HS, ERT	7
Chisholm [32]	2009	Prospective cohort	481	90	< 25, 25–29.9, 30–34.9, ≥ 35	< 30 ≥ 30	311 170	RE-HS, CON	7
Luketina [23]	2014	Retrospective cohort	80	14.7	20–25, ≥ 30	< 30 ≥ 30	40 40	PC, RE-HS, CON	8
Schietroma [24]	2017	Retrospective cohort	201	198	< 25, 25–29.9, ≥ 30	< 30 ≥ 30	132 69	RR, RE-HS, RE-ED, CON	8
Andolfi [25]	2017	Retrospective cohort	176	17	< 30, 30–34.9, ≥ 35	< 30 ≥ 30	111 65	RR	7

Key: RR - Reflux Recurrence, PC - Perioperative complications, RE-HS - Need for re-intervention by redo hiatal surgery, RE-ED - Need for re-intervention by endoscopic dilatation, CON - Laparoscopic to open surgery conversion, ERT - Early return to theatre.

re-intervention by redo surgery [22–24,26–28,30,32] and four reported on the need for re-intervention by endoscopic dilatation [24,26,28,30]. Six studies examined the rate of conversion from laparoscopic to open surgery [23,24,26–28,32], and five reported the rates of early return to theatre [21,22,28,30,31].

3.2. BMI categories

Eight studies opted for a three-cohort design, seven of which comparing outcomes of patients with a BMI < 25, 25–29.9 and ≥ 30 kg/m² [20,24,26,27,29–31], and one comparing outcomes of patients with a BMI < 30, 30–34.9 and ≥ 35 kg/m² [25]. One study reported outcomes for a fourth cohort of morbidly obese patients [32], whilst four studies [21–23,28] opted for a two-cohort design comparing outcomes in non-obese to either obese or morbidly obese patients.

The largest study by Telem et al. (n = 4 231), which utilized a two-cohort design, stratified patients into BMI groups of < 35 and ≥ 35 kg/m² [21]. Although these cohorts did not strictly represent a comparison in outcome between non-obese and obese patients, according to the categories set within this meta-analysis it was felt that the comparison addressed the study's objectives. The meta-analyses were therefore conducted with and without this study to ensure the results were not significantly skewed as a result.

3.3. Operative technique

A variety of laparoscopic fundoplication techniques were described in the eleven studies. Five studies only included patients undergoing laparoscopic Nissen fundoplication [21,22,24,27,31]. Five studies also included patients undergoing anterior partial fundoplication as well as Nissen fundoplications [26,28–30,32], of which 4 included Toupet fundoplication [26,28,30,32]. and one included patients undergoing Belsey Mark IV procedures [29]. Nissen fundoplication remained the operative technique of choice for the clear majority of patients within these five studies. Two studies included more patients undergoing

Toupet fundoplication than Nissen fundoplication [20,23]. One study included Nissen, anterior and posterior fundoplication [25]. A subgroup analysis to investigate the effect of operative technique on outcomes was not possible, because specific procedure numbers were not reported in all studies.

3.4. Reflux symptom recurrence

Twelve studies explored reflux symptom recurrence post LARS, stratified according to BMI [20,22–32]. Six of these studies were excluded due to data not being dichotomous and hence difficult to interpret within the meta-analysis [23,25,26,28–30]. Recurrence of reflux was analysed in the remaining six studies with a median follow up of 47.3 months. One study by Anvari et al. used only subjective measures through direct questioning to define recurrence [22]. Tekin et al. also used clinical symptoms, however all of their recurrences were confirmed with positive pH manometry assessment [26]. Similarly Perez et al. and Schietroma et al. used subjective patient feedback, which was confirmed by either positive endoscopy and/or pH manometry [24,29]. Tsuboi et al. used post-operative endoscopic findings with Los Angeles classification grade A or higher used to define reflux recurrence [20]. Andolfini et al. used barium swallow and pH manometry [25]. The rate of reflux symptom recurrence was lower in non-obese patients than in obese patients post LARS, with meta-analysis demonstrating statistical significance (OR 0.28, 95% C.I. 0.13 to 0.61, p = 0.001) (Fig. 2).

3.5. Perioperative complications

Perioperative complications including intraoperative, immediate and early post-operative complications, were grouped together within the eight studies in which they were reported. Intraoperative complications ranged from bleeding and trocar site complications to pleural tears, liver lacerations, splenic capsular tears, gastric perforation, oesophageal perforation and small bowel perforation [26–28,30]. Post-operative complications included wound infections, urinary tract

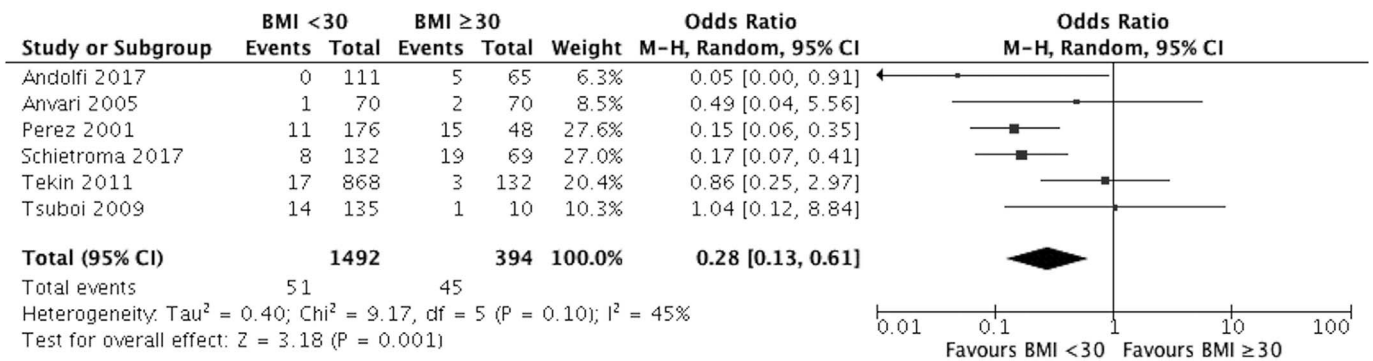


Fig. 2. Recurrence of reflux symptoms post LARS in non-obese and obese patients.

infections, urinary retention, diarrhea, pulmonary related complications (atelectasis, effusion, embolism, pneumonia), deep vein thrombosis, cerebrovascular accidents, cardiac related complications (atrial fibrillation, infarction, arrest), acute kidney injury and early trans-hiatal herniation requiring early return to theatre.

Meta-analysis revealed no statistically significant difference in the rate of perioperative complications between non-obese patients and obese patients (OR 0.82, 95% C.I. 0.54 to 1.23, p = 0.33) (Fig. 3). A further meta-analysis was conducted excluding the Telem et al. study [21], with similar findings (OR 0.76, 95% C.I. 0.44 to 1.33, p = 0.34).

3.6. Need for re-intervention

Meta-analysis revealed no statistically significant difference in the rate of re-intervention by means of redo surgery between non-obese and obese patients (OR 0.94, 95% C.I. 0.51 to 1.72, p = 0.84) (Fig. 4) [22–24,26–28,30,32]. The rate of endoscopic dilatation in the two cohorts was also similar (OR 0.98, 95% C.I. 0.45 to 2.17, p = 0.97) (Fig. 5) [24,26,28,30].

3.7. Conversion from laparoscopic to open surgery

Meta-analysis revealed no statistically significant difference in the rate of conversions from laparoscopic to open surgery (OR 0.96, 95% C.I. 0.50 to 1.85, P = 0.90) (Fig. 6) [23,24,26–28,32].

3.8. Early return to theatre

Meta-analysis of the five studies that reported early return to theatre following LARS again showed no statistically significant difference (OR 0.77, 95% C.I. 0.43 to 1.38, p = 0.39) (Fig. 7) [21,22,28,30,31]. A further meta-analysis was conducted excluding the Telem et al. study again showing no statistically significant difference (OR 0.56, 95% C.I.

0.17 to 1.83, p = 0.33) [21].

3.9. Heterogeneity and publication bias

No statistical heterogeneity was identified in any of the analyses conducted (Table 2). Funnel plots for the studied outcomes were symmetrical suggesting absence of publication bias.

4. Discussion

It is assumed widely and asserted confidently at scientific meetings by certain cohorts of surgeons, that the outcomes of anti-reflux surgery are compromised by abnormally high body mass indices. Obesity is becoming more prevalent, with 15–20% of individuals in Europe fulfilling the criteria of a BMI of greater than 30 kg/m [2], and the situation is far worse in the United States of America [4]. The principal findings of this study question these assumptions. Perioperative outcomes of LARS were similar, regardless of BMI, and these results are testament to the significant advances in pre-operative risk profile assessment, anesthesia, and operative technique made during the last 20 years. Longer term follow up however revealed a higher incidence of recurrent reflux, with a pooled rate of 11.4% in obese patients compared with 3.4% in non-obese patients, raising questions regarding the durability of the repair within these cohorts. A popular and accepted hypothesis for this difference in outcomes is that higher intra-abdominal pressures associated with obesity risks straining or loosening the wrap with the potential for wrap migration upward into the chest [33–35].

The influence of obesity on the development of perioperative morbidity in oesophago-gastric surgery has been widely reported in the literature. Indeed a recent meta-analysis by Wu et al., reporting significantly higher post operative complications in both laparoscopic and open resections for gastric cancer [36–38]. Similarly, obesity has been

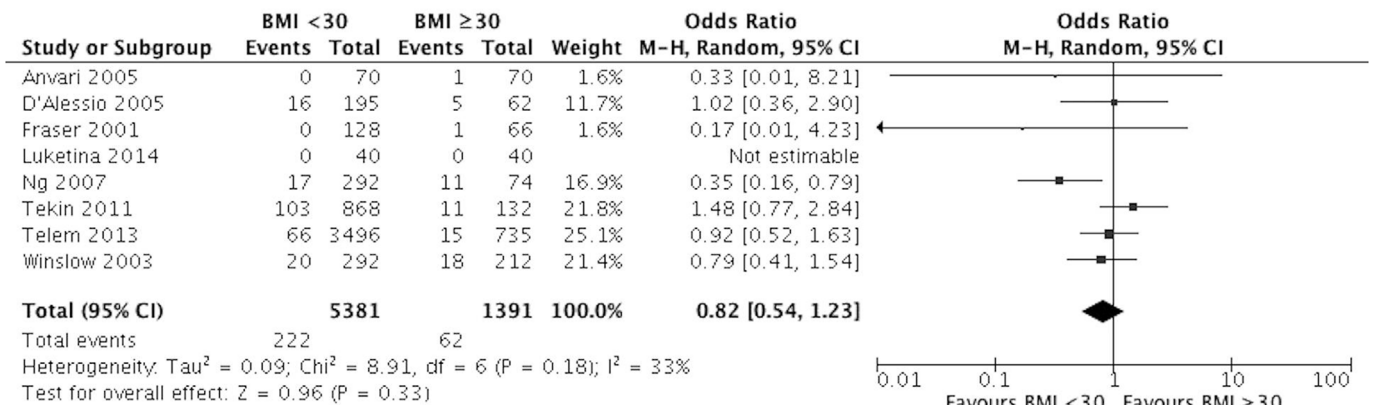


Fig. 3. LARS associated perioperative complications in non-obese and obese patients.

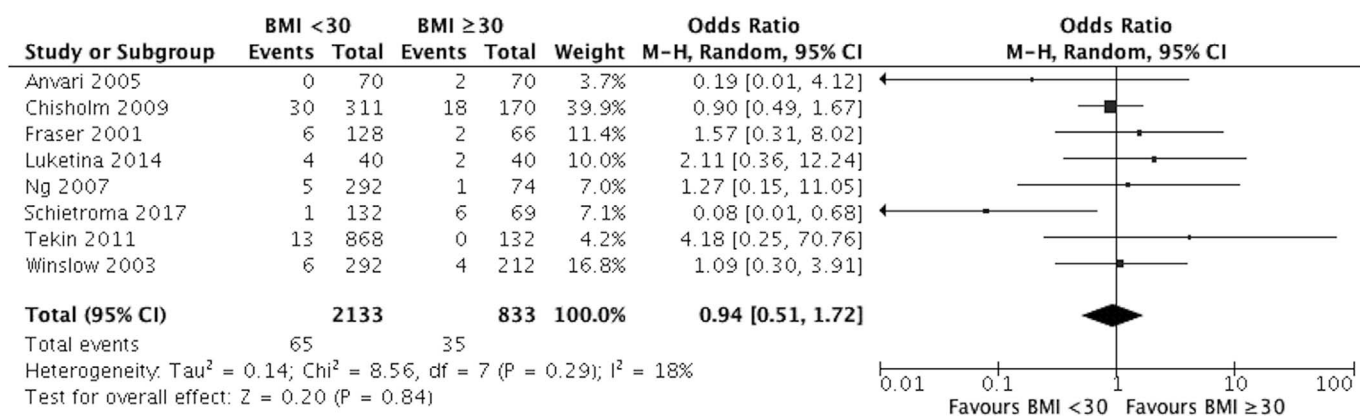


Fig. 4. Re-intervention by redo hiatal surgery post LARS in non-obese and obese patients.

reported to be an independent predictor of conversion to open surgery in a number of laparoscopic procedures, ranging from cholecystectomy to colectorectal resection [39,40]. It is therefore reassuring that despite the apparent, and obvious technical challenges associated with access and retraction at the hiatus, obesity did not appear to confer higher morbidity or rate of open conversion in LARS. On the contrary, many believe that a laparoscopic approach provides unparalleled views of the hiatus, which would otherwise prove challenging to access at open surgery. Rates of re-intervention and redo surgery or endoscopic dilatation were similar regardless of BMI. But caution must be taken when interpreting these findings due to the variety of operative techniques reported. The literature has consistently reported a higher rate of post-operative dysphagia following Nissen fundoplication when compared with partial fundoplication, often necessitating post-operative intervention [13]. As subgroup analysis was not possible due to the wide spectrum of operative approaches reported; this finding represents a potential confounding factor, and bias risk, in the rate of endoscopic dilatations reported in this study.

There are several inherent limitations and potential criticisms of this study in that it is limited by the methodological quality of the studies included. As with all meta-analyses of non-randomized cohort studies, despite not reaching statistical significance, heterogeneity was inevitable due to inherent biases in the pooled studies. Six of the studies included were retrospective cohort studies, meta-analysis of which is prone to confounding bias. The operative technique of choice varied and the measure of reflux recurrence was inconsistent between studies, undoubtedly presenting variability in post-operative outcomes. Other sources of heterogeneity within the results include the lack of stratification in terms of: preoperative reflux severity; the extent of hiatal herniation necessitating repair at surgery; the patient demographics and the surgeon's experience. This and the non-standardized and largely unreported criteria used to select patients for surgery within the studies are further sources of bias. Length of follow up was also inconsistent, as one might expect higher recurrence rates in studies with longer associated clinical follow up.

A strength of the study is the large number of subjects included (6246 non-obese and 1753 obese patients), with all publications analysed deemed high quality as screened by the Newcastle-Ottawa Scale. Recurrence of reflux has been widely reported as being similar in numerous meta-analyses, comparing partial and Nissen funduplications [13–15]. A decision was therefore made to include all operative techniques to improve the power of the analysis.

In conclusion, surgery and anesthesia are more hazardous in patients who are overweight, not least because of the increased incidence of cardiorespiratory comorbidity [41,42]. Moreover, diaphragmatic hiatal surgery can be a painstaking procedure, and is not without its own specific risk when dealing with significant gastric herniation, necessitating careful dissection of the hiatal hernia sac.

5. Conclusions

The findings of this study lend support to LARS, regardless of BMI, and suggest that laparoscopic anti-reflux surgery can be performed safely in obese patients, with strong evidence to suggest equivalent perioperative outcomes when compared with patients of normal body weight. Higher, though modest rates of recurrent reflux however, warrant further investigation in the form of properly constructed, prospective multi-center trials. The role of LARS alongside bariatric surgery in the management of GORD in the morbidly obese, which has been shown to improve symptoms through weight loss and in certain procedures the disruption of normal anatomy, will also need to be further established. In the meantime, clinicians and patients alike should be aware that obesity may adversely affect long term LARS outcome in terms of symptom control, and careful consideration should be given in the consent process inherent within the optimal risk profile assessment of obese patients diagnosed with GORD.

Ethical approval

The authors felt ethical approval was not required for this review

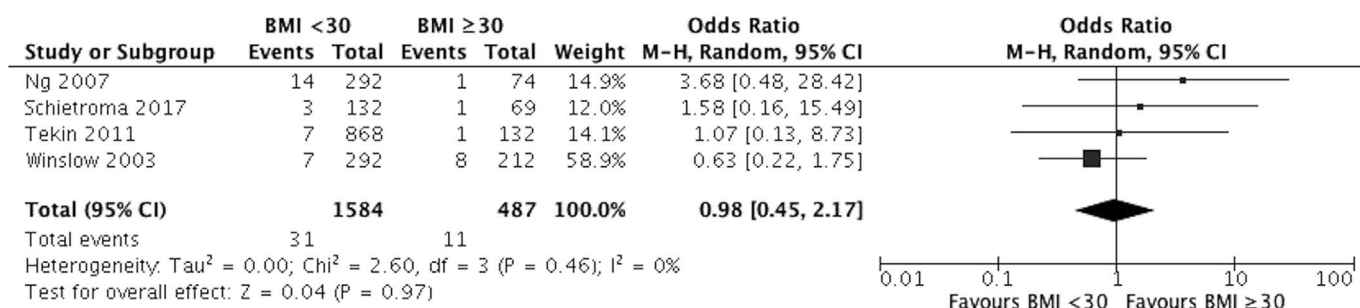


Fig. 5. Re-intervention by endoscopic dilatation post LARS in non-obese and obese patients.

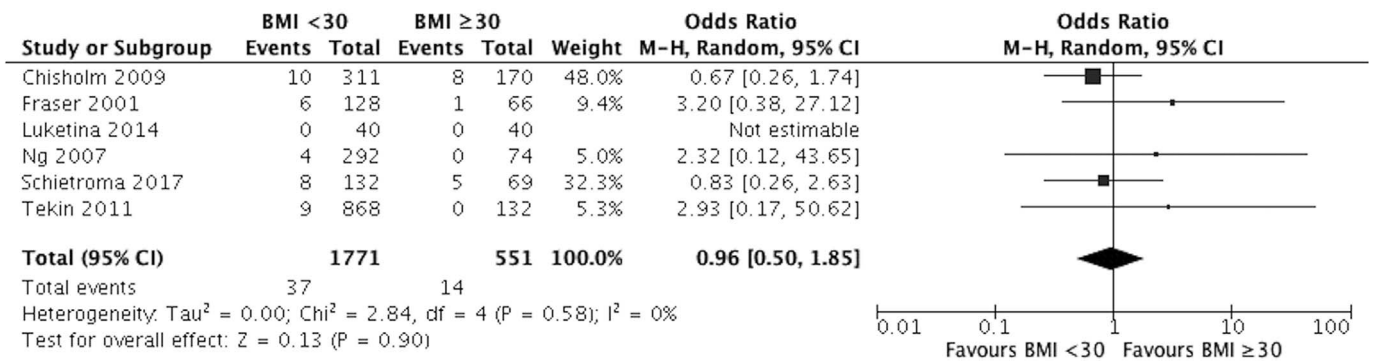


Fig. 6. Conversion from laparoscopic to open surgery in non-obese and obese patients undergoing LARS.

article.

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Author contribution

T Abdelrahman

Conception and design of the work, acquisition, analysis, interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest

Declarations of interest: none.

Trial registry number

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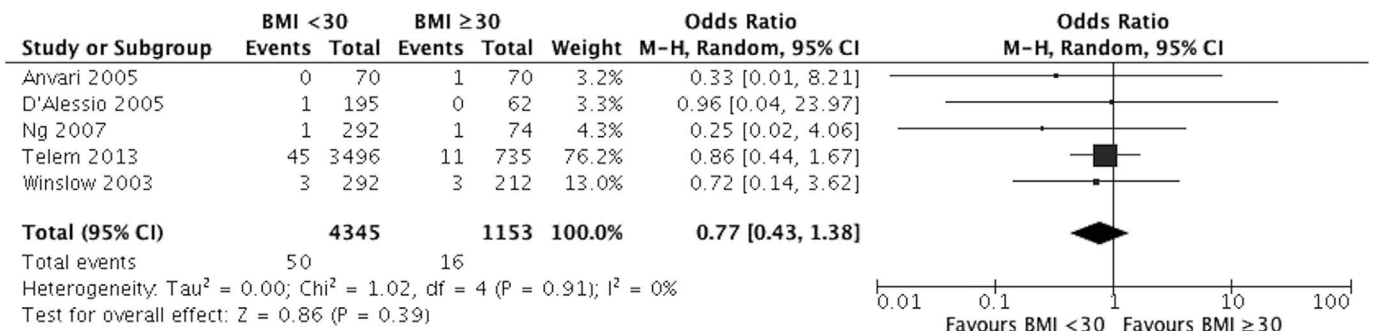


Fig. 7. Early return to theatre post LARS in non-obese and obese patients.

Table 2
Outcomes post LARS stratified by BMI.

	Number of studies	Non-obese (BMI < 30)		Obese (BMI ≥ 30)		Odds Ratio	P	Heterogeneity	
		Events	Total	Events	Total			I ² (%)	P
Recurrence of reflux symptoms	6	51	1492	45	394	0.28 (0.13, 0.61)	0.001	45	0.1
Perioperative complications	8	222	5381	62	1391	0.82 0.54, 1.23)	0.33	33	0.18
Re-intervention by redo hiatal repair	8	65	2133	35	833	0.94 (0.51, 1.72)	0.84	18	0.29
Re-intervention by endoscopic dilatation	4	31	1584	11	487	0.98 (0.45, 2.17)	0.97	0	0.46
Conversion to open surgery	6	37	1771	14	551	0.96 (0.50, 1.85)	0.90	0	0.58
Early return to theatre	5	50	4345	16	1153	0.77 (0.43, 1.38)	0.39	0	0.91

Guarantor

Mr Xavier Escofet.

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