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SAGES REVIEW ARTICLE

Surgical treatment of GERD: systematic review and meta-analysis

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Abstract

Background Gastroesophageal reflux disease (GERD) has a high worldwide prevalence in adults and children. There is uncertainty regarding medical versus surgical therapy and different surgical techniques. This review assessed outcomes of antireflux surgery versus medical management of GERD in adults and children, robotic versus laparoscopic fundoplication, complete versus partial fundoplication, and minimal versus maximal dissection in pediatric patients.

Methods PubMed, Embase, and Cochrane databases were searched (2004–2019) to identify randomized control and non-randomized comparative studies. Two independent reviewers screened for eligibility. Random effects meta-analysis was performed on comparative data. Study quality was assessed using the Cochrane Risk of Bias and Newcastle Ottawa Scale.

Results From 1473 records, 105 studies were included. Most had high or uncertain risk of bias. Analysis demonstrated that anti-reflux surgery was associated with superior short-term quality of life compared to PPI (Std mean difference = −0.51, 95%CI −0.63, −0.40, I^2 = 0%) however short-term symptom control was not significantly superior (RR = 0.75, 95%CI 0.47, 1.21, I^2 = 82%). A proportion of patients undergoing operative treatment continue PPI treatment (28%). Robotic and laparoscopic fundoplication outcomes were similar. Compared to total fundoplication, partial fundoplication was associated with higher rates of prolonged PPI usage (RR = 2.06, 95%CI 1.08, 3.94, I^2 = 45%). There was no statistically significant difference for long-term symptom control (RR = 0.94, 95%CI 0.85, 1.04, I^2 = 53%) or long-term dysphagia (RR = 0.73, 95%CI 0.52, 1.02, I^2 = 0%). Ien, minimal dissection during fundoplication was associated with lower reoperation rates than maximal dissection (RR = 0.21, 95%CI 0.06, 0.67).

Conclusions The available evidence regarding the optimal treatment of GERD often suffers from high risk of bias. Additional high-quality randomized control trials may further inform surgical decision making in the treatment of GERD.

Keywords Antireflux surgery · Fundoplication · Gastroesophageal reflux · Partial fundoplication · Proton pump inhibitor

Gastroesophageal reflux disease (GERD) is a common and costly disease with a high worldwide prevalence. Globally, millions of individuals are affected, with up to 27% of North American adults afflicted with GERD [1]. While the frequency of GERD in children is difficult to estimate, up to 6% of children may also be affected [2]. GERD is the number one gastrointestinal diagnosis among outpatient visits in the United States, with nearly one million visits annually. The cost of GERD treatment is also significant, with over $10 billion spent annually on proton-pump inhibitors, the

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primary medical treatment for GERD [3]. Individuals suffering from GERD have reduced quality of life including decreased work productivity [4, 5].

Proton pump inhibitors (PPI) are often recommended as the first-line treatment for GERD [6]. While PPIs are effective in resolving erosive esophagitis secondary to reflux of gastric secretions into the esophagus, many patients continue to suffer from reflux symptoms [7]. Additionally, there is increasing concern about the long-term consequences of indefinite PPI use including vitamin and electrolyte deficiencies, fractures, pneumonia, and *C. Difficile* infection [8–12]. To this point, a recent Cochrane review attempted to weigh the risks and benefits of chronic PPI use, though a robust recommendation could not be made due to low to moderate quality of available evidence [13].

Antireflux surgery offers an alternative to medical therapy that may minimize chronic PPI use and its associated risks. Antireflux procedures mechanically augment the lower esophageal sphincter to prevent abnormal reflux of gastric contents into the esophagus [14, 15]. Both medical and surgical guidelines recognize antireflux surgery as an effective treatment for GERD in appropriate patients [6, 16, 17]. Unfortunately, many comparative studies on the treatment of GERD involve small patient numbers or derive from single institution experiences, sometimes resulting in discordant results.

Reasons that may lead to suboptimal outcomes after antireflux surgery include inadequate pre-operative evaluation, poor patient and procedure selection, or suboptimal technique [18]. Optimizing surgical outcomes is therefore critical, to minimize the percentage of patients who continue to suffer GERD symptoms after operative intervention. Technical considerations such as whether to perform partial versus total fundoplication, divide the short gastric vessels or not, or whether to incorporate new robotic approaches may affect the effectiveness of antireflux surgery and need to be evaluated in a systematic fashion [19–21].

To address these issues of comparative effectiveness of antireflux surgery and impact of technical variation on patient outcomes, and to inform updated SAGES guidelines, we conducted a systematic review and meta-analysis to pool data when possible and better inform the care of the millions of individuals suffering from GERD.

Methods and materials

Members of the SAGES guidelines committee performed a systematic review and meta-analysis according to the PRISMA guidelines [22] to compare different medical and surgical interventions in the treatment of GERD. The systematic review group created four key questions according to the PICO format (Population, Intervention, Comparator, and Outcomes) to guide our literature search, with the questions structured as follows and outcomes listed separately:

Key question 1 (KQ1) Fundoplication versus Medical management in adult and pediatric patients with GERD.

Key question 2 (KQ2) Robotic versus Laparoscopic Fundoplication in adult and pediatric patients with GERD.

Key question 3 (KQ3) Complete versus Partial Fundoplication in adult and pediatric patients with GERD.

Key question 4 (KQ4)

(a) Division of short gastrics versus No division of short gastrics in adult patients with GERD

(b) Minimal dissection versus Maximal dissection in pediatric patients with GERD

Literature search & eligibility criteria

With the assistance of a professional librarian, a clinically guided search of PubMed, Embase, and Cochrane databases was performed for each key question in February 2019. An example of the full search criteria for key question 1 is provided in Table 4 in Appendix 1. The search was restricted to human studies between 2004 and 2019. Eligible study types included randomized control trials (RCT) and non-randomized comparative study designs. All records were combined on EndNote (Clarivate Analytics) then uploaded to Covidence [23] for screening. Duplicates were automatically removed in both EndNote and Covidence prior to screening. A search update was completed in April 2020 to capture more recent studies or studies not included in the original search.

Study selection

Before review of all identified abstracts, reviewers' ratings were calibrated by having all reviewers review the same, randomly selected 50 abstracts on Abstrackr (Brown University, Providence, Rhode Island) and discuss any disagreements during a conference call. After this reviewer calibration, each title and abstract were screened each by two reviewers for relevance and eligibility on Covidence. Publications irrelevant to the key questions, remaining duplicates, and non-English language studies were excluded. The full text of all relevant articles were then reviewed during which non-comparative studies, case reports, letters to the editor, lay press articles, abstracts, author replies, and reviews were excluded from pooled analysis. Only full, peer-reviewed, English language manuscripts pertinent to the key questions above were included. Handsearching was also performed

during full text review by checking the reference lists of systematic reviews and included studies for additional relevant references. Handsearching was not limited to the same date restrictions as the database search if a relevant comparative study was found. Both abstract and title screening as well as full text review on Covidence were performed by two investigators, with any discrepancies resolved by a third investigator and discussion among the reviewers.

Risk of bias in individual studies

The Cochrane Risk of Bias tool was used to assess the risk of bias for included randomized control trials [24]. Two investigators scored each RCT on the following criteria: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete data, non-comparable groups, performance bias, and detection bias. Quality assessment of non-randomized studies was evaluated using the Newcastle–Ottawa Scale [25]. Two investigators scored each non-randomized study on selection bias, comparability of groups, and outcome reporting. A final risk of bias assessment was determined for each RCT and non-randomized study, with discrepancies in quality reporting resolved by discussion and a third investigator. Risk of bias was sought to assess the overall quality of the evidence and also to investigate whether significant heterogeneity during meta-analysis could be explained by a difference in study risk of bias. When there was significant heterogeneity noted between high and low risk of bias studies, they were presented separately.

Data extraction

Data extraction forms on Covidence included study characteristics, methods, population, interventions, and a priori determined outcomes. Two investigators independently completed the form for each included study. Outcomes included quality of life, symptom control (gastroesophageal reflux), proton pump inhibitor use, objective measures of esophageal acid such as DeMeester score and pH normalization, long-term dysphagia, long-term gas bloat symptoms and dumping symptoms, surgical complications including Clavien-Dindo grades 3–4 [26], readmission, hospital length of stay, wrap failure requiring reoperation, endoscopic dilation, and costs. For pediatric studies, weight gain and readmission for respiratory causes were also extracted when present.

Analysis

Random effects meta-analysis was performed in RevMan (Version 5.3.5) [27], using Mantel–Haenszel Odds ratio (RR) for binary outcomes and inverse variance weighted mean difference for continuous outcomes. For continuous outcomes using multiple scales, a standardized mean difference (SMD) was used. Heterogeneity between studies was assessed using measures of I^2 and χ^2. All comparative studies, including observational and high risk of bias, are presented, but results and conclusions focus on randomized controlled trials and low risk of bias studies when available.

Results

From both database searching and hand searching, a total of 1473 records were screened. Ultimately, 102 unique studies relevant to the 4 key questions were included. Screening results, including reasons for exclusion during full text review, are demonstrated in a modified PRISMA flow diagram in Fig. 1. The characteristics for the included studies are shown in Table 1.

Key question 1

A total of 36 studies met inclusion criteria for KQ1 (medical versus surgical management of GERD), composed of 20 RCTs, 13 cohort studies, and 3 studies modeling costs of PPI versus surgical treatment for GERD using Markov models which were summarized given limited cost data from comparative studies [28–30].

Risk of bias

Of the 13 cohort studies, three (23%) were determined to have a low risk of bias, eight (62%) had a high risk of bias, and the remaining two (15%) had an unclear risk of bias. Of the 20 RCTs, seven (35%) had low overall bias, nine (45%) had a high bias, and four (20%) had unclear bias. Risk of bias assessments for individual cohort and randomized controlled trials are shown in Supplemental Figures S1 and S2, respectively.

Adults Short-term (< 5 year) quality of Life (QOL): Four RCTs reported on short-term QOL comparing medical (575 total patients) and surgical (594 total patients) treatment of GERD [31–34]. These studies demonstrated worse QOL with PPI (SMD = −0.51, 95%CI −0.63, −0.40) with low heterogeneity (I^2 = 0%) (Fig. 2). Two cohort studies also reported on short-term quality of life (QOL) comparing medical and surgical management of GERD [35, 36]. There was no statistically significant difference in short-term QOL.

Long-term (> 5 year) quality of life (QOL): Three RCTs reported on long-term QOL comparing medical and surgical treatment of GERD, including 282 patients treated with PPI and 227 patients undergoing operative intervention [37–39] (Fig. 3). Pooled analysis did not demonstrate a difference (SMD = 0, 95%CI −0.23, 0.23, I^2 = 35%). Given the

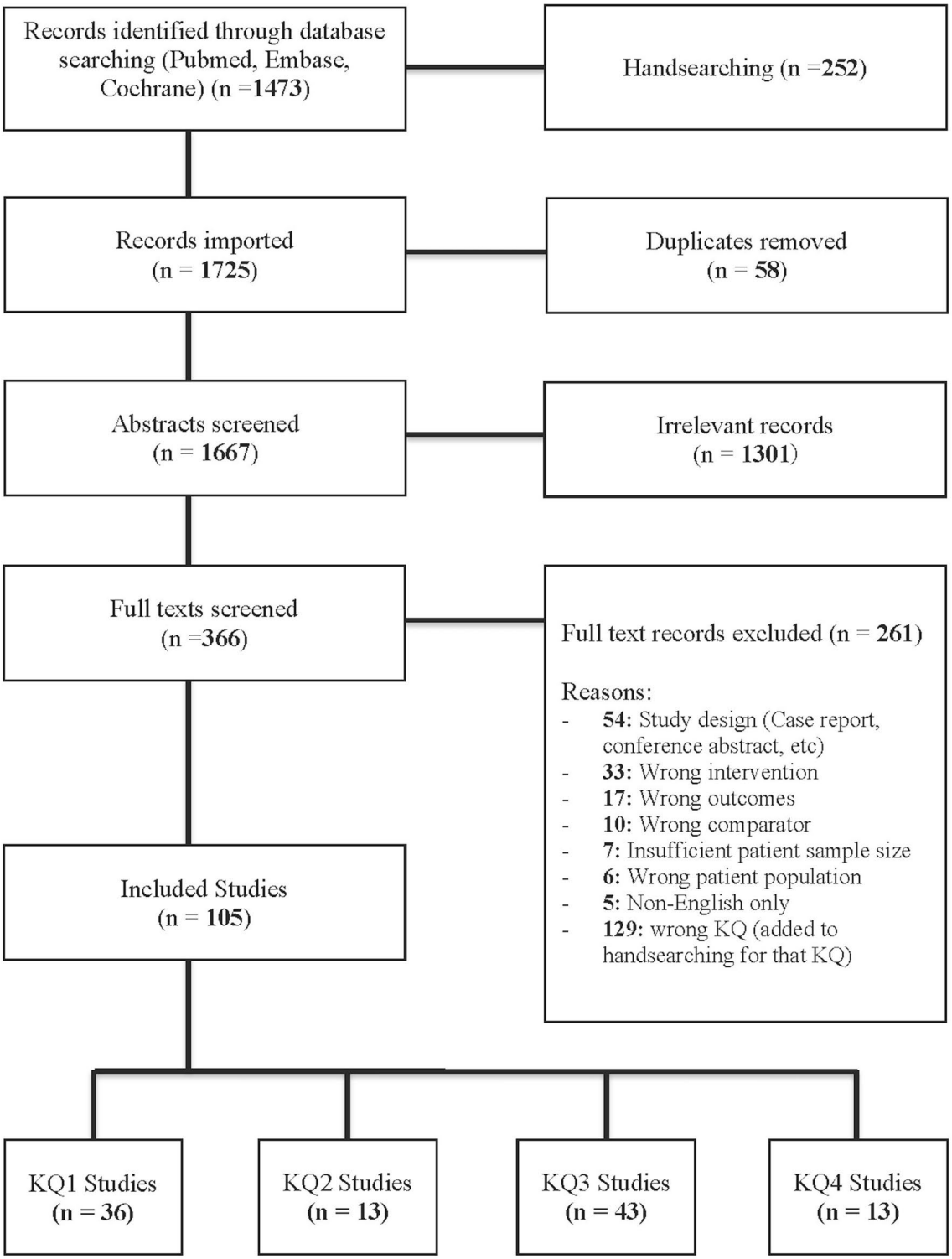

Fig. 1 Modified PRISMA flow diagram demonstrating the search results for all 4 key questions. Duplicates removed on endnote are not shown

heterogeneity of time points and scales used to report long-term QOL after medical or surgical treatment for GERD, subgroup analyses by type of QOL scale and time point are presented in Supplemental Figure S3 and Figure S4.

pH normalization: Four RCTs reported on pH normalization comparing patients undergoing medical ($n = 318$) versus surgical treatment ($n = 254$) of GERD [34, 39–41]. Patients treated medically had more abnormal pH exposure

Table 1 Summary of included studies, including country of origin, adult vs pediatric population, and number of study participants

References	Type of study	Country	Adult or pediatric	*n*
Key question 1: surgical versus medical management of GERD				
Anvari et al. [31]	RCT	Canada	Adult	104
Anvari et al. [40]	RCT	Canada	Adult	104
Arguedas et al. [30]	Markov simulation	USA	Adult	n/a
Attwood et al. [55]	Cohort	UK	Adult	45
Attwood et al. [130]	RCT	Sweden, Norway, UK, Germany, France, Italy	Adult	60
Babar et al. [131]	Case–control	Ireland	Adult	37
Bojke et al. [28]	Markov simulation	UK	Adult	n/a
Ciovica et al. [35]	Cohort	Austria	Adult	579
Epstein et al. [29]	Markov simulation	UK	Adult	n/a
Esposito et al. [57]	Cohort	Italy	Pediatric	36
Fiocca et al. [132]	RCT	11 European countries	Adult	514
Galmiche et al. [47]	RCT	11 European countries	Adult	372
Goeree et al. [52]	RCT-based cost analysis	Canada	Adult	104
Grant et al. [32]	RCT	UK	Adult	357
Grant et al. [51]	RCT	UK	Adult	810
Grant et al. [37]	RCT-based cost analysis	UK	Adult	810
Grant et al. [133]	RCT	UK	Adult	810
Gurski et al. [134]	Cohort	USA	Adult	91
Hatlebakk et al. [41]	RCT	Norway	Adult	267
Lundell et al. [38]	RCT	Sweden	Adult	255
Lundell et al. [48]	RCT	Sweden	Adult	218
Lundell et al. [33]	RCT	11 European Countries—LOTUS trial	Adult	554
Lundell et al. [45]	RCT	11 European Countries—LOTUS trial	Adult	124
Mahon et al. [34]	RCT	UK	Adult	217
Mauritz et al. [135]	Cohort	Netherlands	Pediatric	25
Mehta et al. [44]	RCT	UK	Adult	183
Parrilla et al. [46]	RCT	Spain	Adult	101
Rantanen et al. [50]	Case series	Finland	Adult	213
Rossetti et al. [36]	Cohort	Italy	Adult	301
Rossi et al. [53]	Cohort	Italy	Adult	35
Spechler et al. [39]	RCT	USA	Adult	366
Spechler et al. [17]	RCT	USA	Adult	239
Swoger et al. [43]	Cohort	USA	Adult	72
Tolone et al. [42]	Case–control	Italy	Adult	37
VanMeer et al. [49]	Cohort	Netherlands	Adult	477
Zaninotto et al. [54]	Cohort	Italy	Adult	89
Key question 2: laparoscopic vs robotic fundoplication				
Albassam et al. [67]	Cohort	Saudi Arabia	Pediatric	50
Anderberg et al. [68]	Cohort	Sweden	Pediatric	12
Anderberg et al. [70]	Cohort	Sweden	Pediatric	24
Broeders et al. [93]	RCT	Netherlands	Adult	167
Ceccarelli et al. [60]	Cohort	Italy	Adult	137
Draaisma et al. [58, 62]	RCT	Netherlands	Adult	50
Hartmann et al. [61]	Cohort	Germany	Adult	80
Lehnert et al. [66]	Cohort	Germany	Pediatric	20
Morino et al. [63]	RCT	Italy	Adult	50
Muller-Stitch et al. [21]	RCT	Germany	Adult	40
Muller-Stitch et al. [59]	RCT	Germany	Adult	40
Nakadi et al. [65]	RCT	Belgium	Adult	20

Table 1 (continued)

References	Type of study	Country	Adult or pediatric	*n*
Owen et al. [64]	Cohort	USA	Adult	12,079
Key question 3: complete vs partial fundoplication				
Aye et al. [79]	RCT	USA	Adult	102
Baigrie et al. [100]	RCT	South Africa	Adult	163
Booth et al. [71]	RCT	UK	Adult	127
Broeders et al. [93]	Cohort	Australia	Adult	2040
Broeders et al. [105]	Case–control	Netherlands	Adult	42
Broeders et al. [19]	RCT	Australia	Adult	18
Cai et al. [103]	RCT	Australia	Adult	89
Cao et al. [72]	RCT	China	Adult	100
Djerf et al. [73]	RCT	Sweden	Adult	72
Esposito et al. [107]	Cohort	Italy, France, Netherlands	Pediatric	238
Fernando et al. [84]	Cohort	USA	Adult	206
Goessler et al. [98]	Cohort	Austria	Pediatric	44
Guerin et al. [101]	RCT	Belgium	Adult	140
Gunter et al. [104]	Cohort	USA	Adult	316
Hakanson et al. [78]	RCT	Sweden	Adult	456
Hoshino et al. [83]	Cohort	Japan	Adult	401
Khan et al. [81]	RCT	UK	Adult	121
Koch et al. [95]	RCT	Austria	Adult	100
Koch et al. [96]	RCT	Austria	Adult	100
Koch et al. [136]	RCT	Austria	Adult	125
Kubiak et al. [109]	RCT	UK	Pediatric	167
Ludemann et al. [137]	RCT	Australia	Adult	101
Mickevicius et al. [80]	RCT	Lithuania	Adult	153
Mickevicius et al. [87]	RCT	Lithuania	Adult	129
Mucio et al. [74]	RCT	Mexico	Adult	512
Nijjar et al. [88]	RCT	Australia, New Zealand	Adult	112
Pessaux et al. [90]	Cohort	France	Adult	2684
Qin et al. [102]	RCT	China	Adult	383
Radajewski et al. [92]	Cohort	Australia	Adult	94
Robertson et al. [99]	Cohort	UK	Adult	246
Roks et al. [89]	RCT	South Africa	Adult	90
Ruiz-Tovar et al. [85]	Cohort	Spain	Adult	106
Shaw et al. [97]	RCT	South Africa	Adult	100
Spence et al. [75]	RCT	Australia	Adult	79
Stewart et al. [94]	Cohort	UK	Adult	357
Strate et al. [76]	RCT	Germany	Adult	200
Toydemir et al. [86]	Cohort	Turkey	Adult	1000
Wagener et al. [108]	Cohort	UK	Pediatric	144
Walle et al. [138]	Cohort	USA	Adult	255
Wang et al. [106]	RCT	China	Adult	84
Watson et al. [77]	RCT	Australia, New Zealand	Adult	112
Wykypiel et al. [91]	Cohort	Austria	Adult	77
Zingg et al. [82]	Cohort	Switzerland	Adult	873
Key question 4: division vs no division of short gastric vessels (adults), minimal vs maximal dissection (children)				
Blomqvist et al. [111]	RCT	Sweden	Adult	99
Chrysos et al. [112]	RCT	Greece	Adult	56
Desai et al. [120]	RCT	USA	Pediatric	80
Farah et al. [113]	RCT	Brazil	Adult	90

Table 1 (continued)

References	Type of study	Country	Adult or pediatric	*n*
Gad El-Hak et al. [139]	Cohort	Egypt	Adult	150
Ielpo et al. [115]	Cohort	Spain	Adult	123
Kinsey-Trotman et al.[20]	RCT	Australia	Adult	102
Kosek et al. [117]	RCT	Austria	Adult	41
Mardani et al. [110]	RCT	Sweden	Adult	99
O'Boyle et al. [118]	RCT	Australia	Adult	102
St Peter et al. [119]	RCT	USA	Pediatric	177
Watson et al. [114]	RCT	Australia	Adult	102
Yang et al. [140]	RCT	Australia	Adult	102

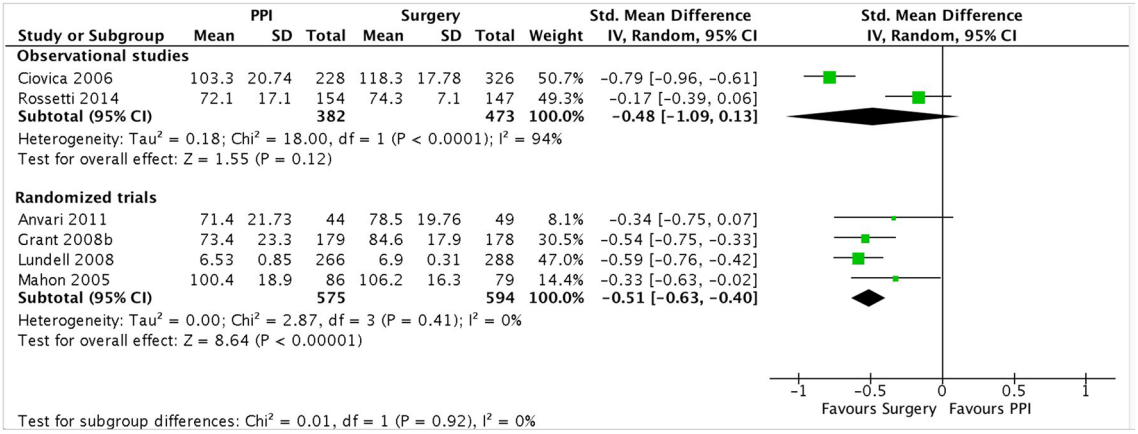

Fig. 2 Short-term quality of life in studies comparing surgery to medical treatment. (< 5-year follow-up)

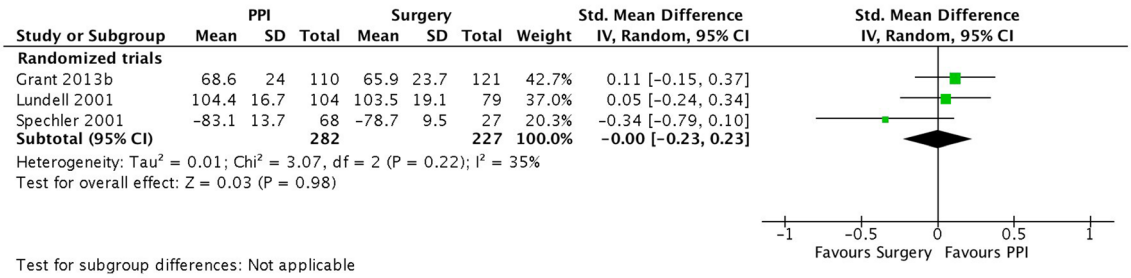

Fig. 3 Long-term quality of life in studies comparing surgery to medical treatment. (> 5-year follow-up)

than patients treated surgically (Mean difference = 2.11, 95%CI 1.83, 2.38, $I^2 = 0\%$) (Fig. 4). A RCT with data on DeMeester scores also favored surgery, with patients on PPI demonstrating higher DeMeester scores than patients treated surgically (Mean difference = 9.0, 95%CI 3.25, 14.95) [34]. Two small observational studies with data on measures of pH normalization also support the superiority of surgery relative to PPI treatment [42, 43].

Short-term (< 5 years) symptom control: One low risk of bias and two high risk of bias RCTs report on short-term symptom control between patients treated medically ($n = 202$) versus surgically ($n = 207$) for GERD [17, 37, 40] (Fig. 5). Together, they demonstrate fewer patients on PPI achieved short-term symptom control relative to the surgical group, though this was not statistically significant and there was significant study heterogeneity not explained by study risk of bias (RR = 0.75, 95%CI 0.47, 1.21, $I^2 = 82\%$).

Long-term (> 5 years) symptom control: Five RCTs were pooled to compare long-term symptom control between patients undergoing medical ($n = 378$) versus

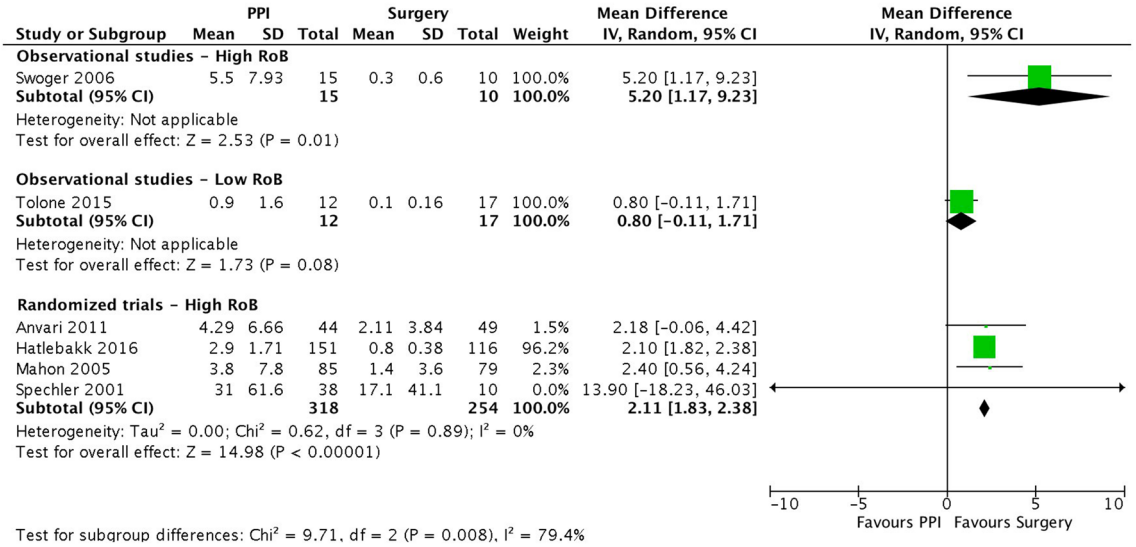

Fig. 4 Normalization of pH for surgery versus medical therapy

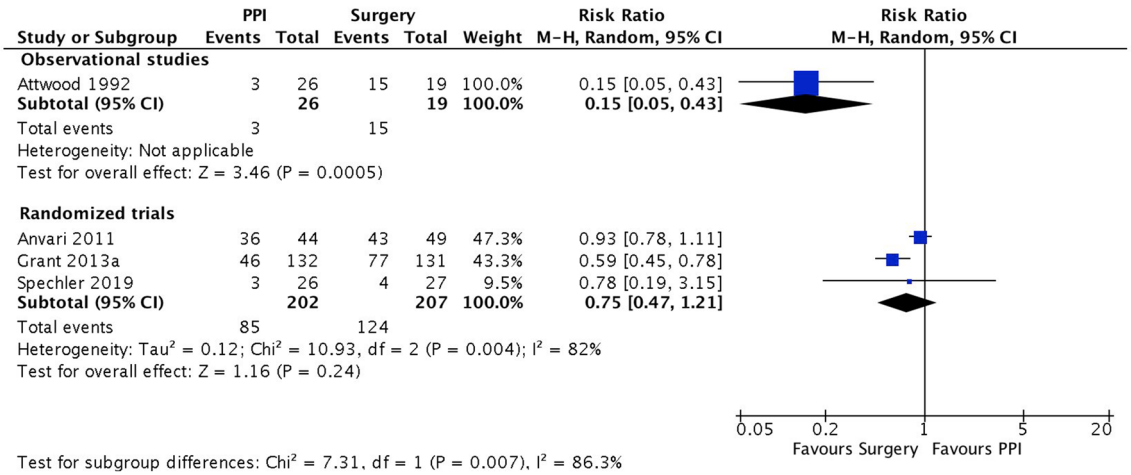

Fig. 5 Short-term symptom control (< 5 years follow-up) for surgery compared to medical therapy

surgical treatment ($n = 370$) [37, 41, 44–46] (Fig. 6). There was improved long-term symptom control in patients undergoing surgery, though there was significant study heterogeneity (RR = 0.79, 95%CI 0.63, 0.999, $I^2 = 87\%$). The one high quality RCT did not find a difference in long-term symptom control between patients treated medically or surgically for GERD [46].

Complications: Five RCTs compared complications for patients undergoing medical versus surgical treatment for GERD [33, 37, 39, 40, 46]. Three RCTS with high risk of bias included 497 patients treated with PPI and 478 patients treated with surgery and slightly favored PPI use (RR = 0.67, 95%CI 0.46, 0.98, $I^2 = 0\%$) (Fig. 7). Two low risk of bias RCT studies found no statistically significant difference in complication rates between medical ($n = 69$) and surgical ($n = 85$) therapy (RR = 1.40, 95%CI 0.29, 6.69, $I^2 = 35\%$).

Long-term (> 5 years) dysphagia: Five RCTs compared long-term dysphagia between patients receiving medical ($n = 628$) or surgical ($n = 600$) treatment for GERD and found no difference in rates of dysphagia, although there was significant heterogeneity (RR = 0.92, 95%CI .50, 1.67, $I^2 = 61\%$) [32, 39, 46–48] (Fig. 8).

Long-term (> 5 years) PPI use: Three RCTs from three different countries compared prolonged PPI usage between patients treated medically ($n = 363$) or surgically ($n = 308$) for GERD [37–39] (Fig. 9). As expected, patients treated with PPI were significantly more likely to require prolonged PPI use relative to the patients undergoing surgery (RR = 2.57, 95%CI 1.31, 5.02), though there was

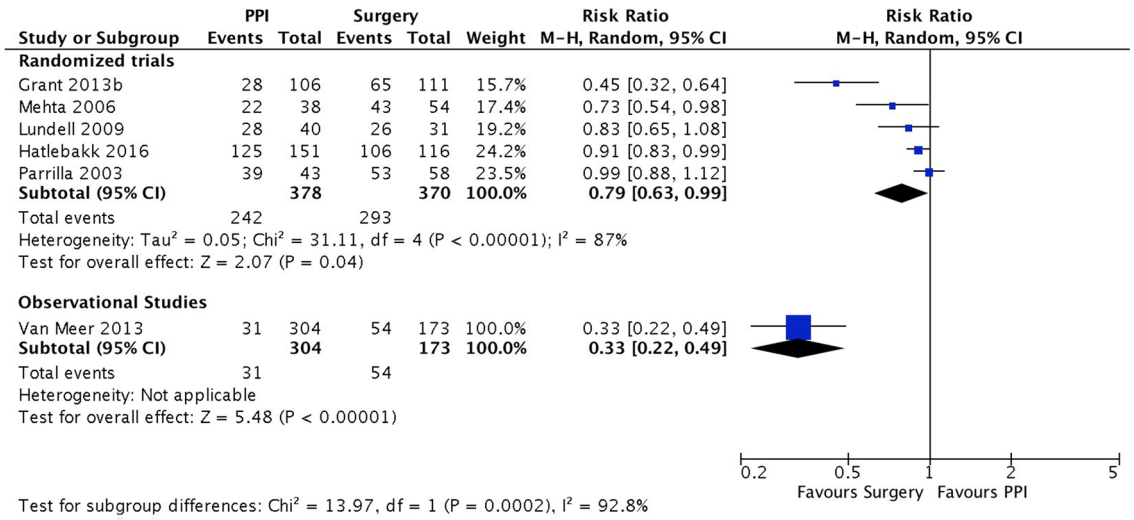

Fig. 6 Long-term symptom control (> 5 years follow-up) for surgery compared to medical therapy

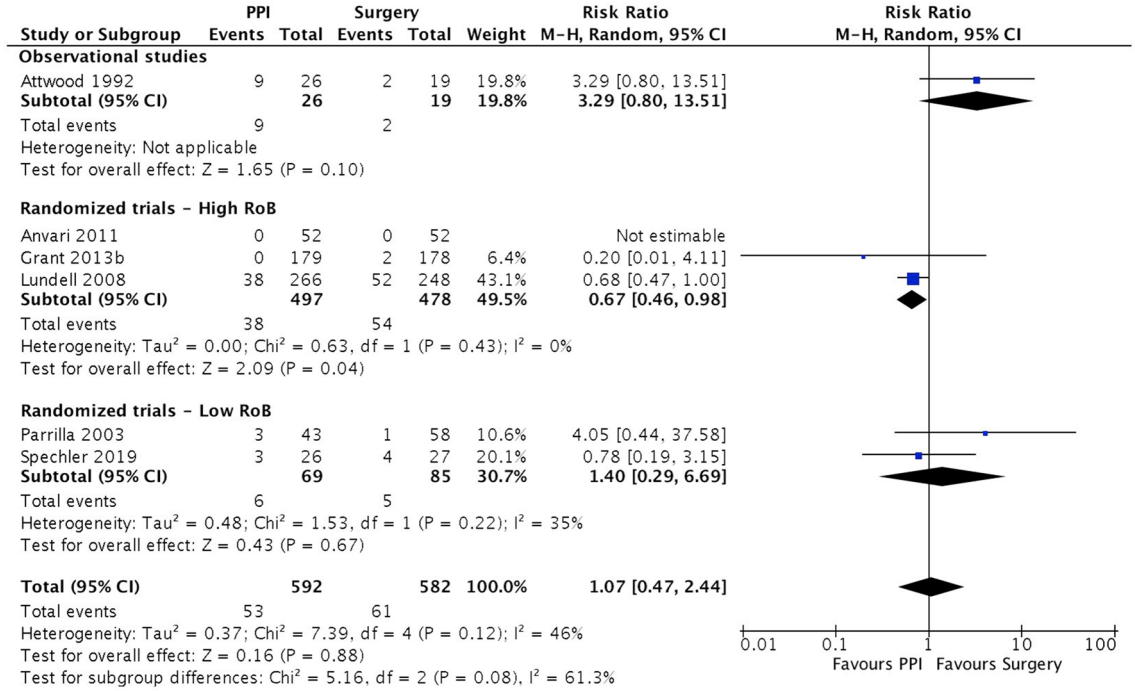

Fig. 7 Complications for surgery compared to medical therapy

significant study heterogeneity ($I^2 = 92\%$) not explained by study quality. Importantly, 86 of the 308 patients (28%) randomized to surgical intervention still reported prolonged PPI use. A single, high risk of bias, retrospective cohort study demonstrated similar results, with higher rates of long-term PPI use among patients who pursued medical, rather than surgical, treatment of GERD [49].

Remaining results: A number of additional outcomes were reported by a small number of studies (Supplemental Table S1). In the LOTUS trial, 266 patients treated with PPI were compared to 288 patients randomized to treatment with surgery [47]. Investigators found no difference in rates of long-term dumping (RR = 0.94, 95%CI 0.64, 1.39), however patients who received medical therapy were significantly less

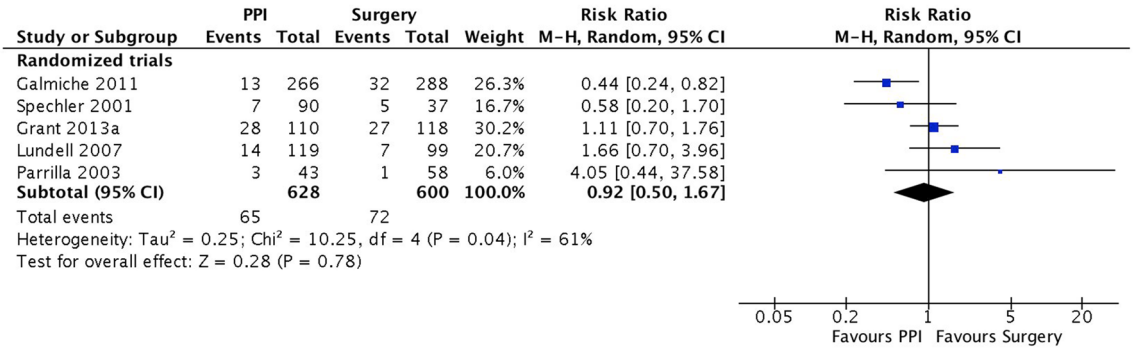

Fig. 8 Long-term (> 5 years) dysphagia for surgery compared to medical therapy

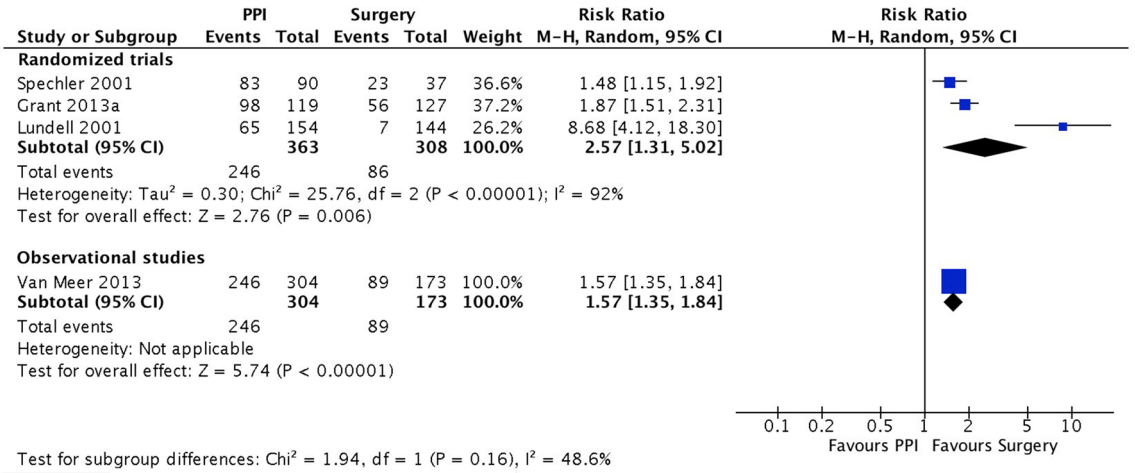

Fig. 9 Long-term PPI use for medical treatment with PPI versus surgery

likely to report long-term bloating (RR = 0.70, 95%CI 0.55, 0.89). One cohort study and one randomized study compared rates of pneumonia in adult patients treated medically versus surgically for GERD; both studies indicated that patients on PPI suffered higher rates of pneumonia, though neither study found that this difference was statistically significant [39, 50]. Treatment failure was reported by two RCTs including 269 patients undergoing PPI treatment and 216 patients undergoing operative intervention [39, 51]. There was no significant difference in treatment failure rates between the two groups (RR = 0.52, 95%CI 0.22, 1.25, $I^2 = 0\%$).

Five studies compared cost of PPI versus surgical intervention for GERD, and all five found surgical treatment to be more expensive than PPI treatment (Supplemental Table S2) [28–30, 51, 52]. Three of these studies used Markov modeling to simulate cost, finding PPI to be cheaper than surgical intervention. Two studies used real cost data from randomized control trial data to compare short-term costs of PPI treatment versus surgical treatment, again finding PPI was less costly than surgical intervention. Despite increased raw cost, surgical treatment was judged to be cost effective in three of the five studies given its association with improved quality of life relative to medical treatment [28, 29, 52].

Barrett's esophagus: Barrett esophagus, replacement of squamous to columnar epithelium, is a complication of GERD and is a risk factor for the development of adenocarcinoma. Four cohort studies and one RCT compare the effect of medical treatment versus surgical therapy in patients with Barrett esophagus [42, 53–55] (Fig. 10). These demonstrated superiority of antireflux surgery over medical treatment for the regression of Barrett's, although this did not reach statistical significance (RR = 1.13, 95%CI 0.92, 1.39, $I^2 = 50\%$). While the RCT did not show a difference in the progression of Barrett's to dysplasia or carcinoma between the two therapies, there was a significant decrease in the median percentage of total time with pH below 4 in the antireflux surgery group. Attwood et al. also found superiority in the control of symptoms of antireflux surgery over pharmacological acid suppression which was consistent with the other RCT data demonstrated in our analysis [55].

Pediatrics: The absence of comparative studies in the pediatric population evaluating medical versus surgical

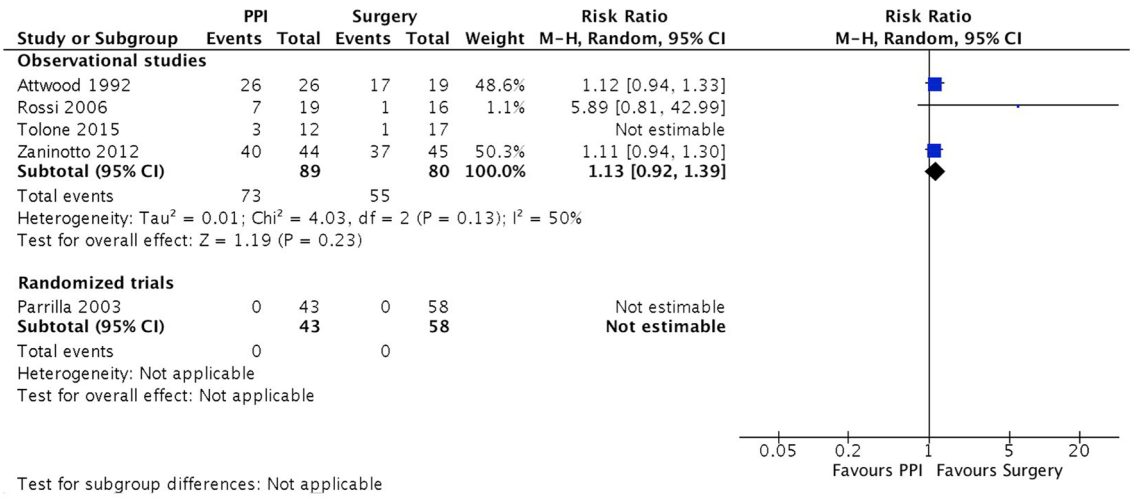

Fig. 10 Barrett's (regression or progression) for surgery compared to medical therapy

management for GERD precluded analysis. However, two single arm studies of greater than 25 pediatric patients are summarized narratively. One single arm study showed that fundoplication significantly decreased reflux symptoms and total acid exposure time in 25 patients three months after surgery [56]. Another long-term study of 36 patients with over ten year follow-up demonstrated that laparoscopic fundoplication produced a good clinical result and a good quality of life [57].

Key question 2

A total of 13 studies met the inclusion criteria for KQ2 (laparoscopic versus robotic fundoplication), which included 6 RCTs and 7 cohort studies.

Risk of bias

Of the six RCTs, three were determined to have low overall risk of bias, one had high overall risk of bias, and two had unclear risk of bias. Of 7 cohort studies, two were determined to have a low risk of bias, four had a high risk of bias, and the remaining study was determined to have an unclear risk of bias. Risk of bias for individual RCT and cohort studies are indicated in Supplemental Figs. 5 and 6, respectively.

Adults Symptom control: Two RCTs addressed symptom control, with 45 patients randomized to robotic fundoplication and 45 patients randomized to laparoscopic fundoplication [58, 59] (Fig. 11). There was no difference found in symptom control between robotic fundoplication and laparoscopic fundoplication (RR = 0.95, 95%CI0.85, 1.07, $I^2 = 0\%$). Two cohort studies compared GERD symptom

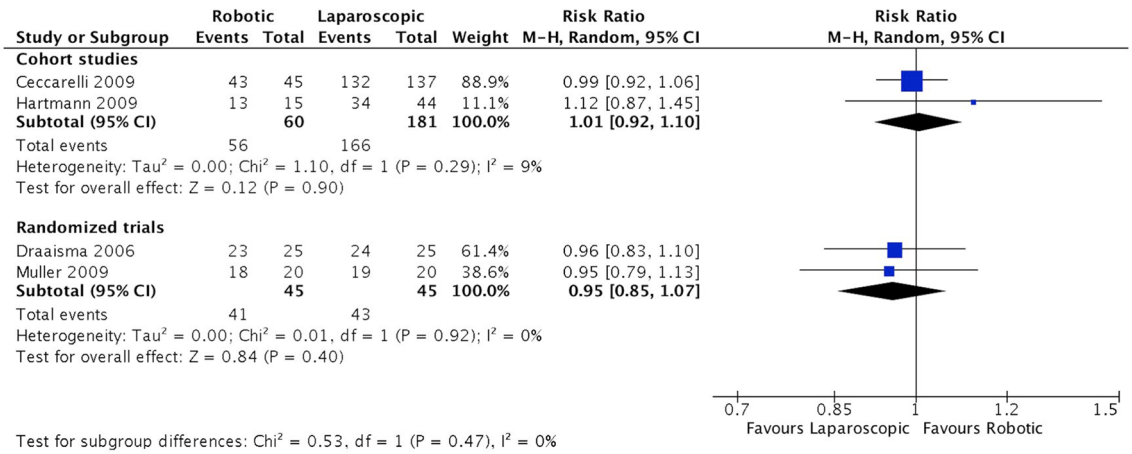

Fig. 11 Symptom control for laparoscopic compared to robotic fundoplication

control between robotic and laparoscopic fundoplication [60, 61]. Symptom control was reported as Visick score I or II (symptoms resolved or improved) [60] and patient rating of intervention success as satisfactory or complete/good [61]. Overall there was no difference between robotic and laparoscopic fundoplication for symptom control in these two studies.

Complications (Clavien-Dindo ≥ 3): Three RCTs with 140 patients randomized to either robotic or laparoscopic fundoplication reported the rate of complications and meta-analysis demonstrated no difference in complication rate (RR = 1.34, 95%CI 0.27, 6.70, I^2 = 0%) [59, 62, 63] (Fig. 12). Three cohort studies compared complication rates between robotic (n = 402) and laparoscopic (n = 9771) surgery [60, 61, 64]. The complication rate was no different between robotic and laparoscopic fundoplication.

Cost: Four studies compared the cost of robotic fundoplication to laparoscopic fundoplication. All studies found robotic fundoplication to be costlier regardless of whether perioperative, inpatient, or yearly investment and maintenance were compared [21, 63–65] (Table 2).

Postoperative length of stay: With regard to postoperative length of stay, we identified three RCTs including 54 patients undergoing robotic fundoplication and 56 undergoing laparoscopic fundoplication [59, 63, 65]. Overall, there was no difference in length of stay (Mean difference in days = −0.07, 95%CI −0.51, 0.38, I^2 = 31%). Three cohort studies compared postoperative length of stay between the two approaches and also found no difference [60, 61, 64].

Remaining results: For several outcomes including DeMeester scores, pH monitoring, PPI use, and wrap failure, only single RCT or cohort studies were identified, and pooled analysis was not possible (Supplemental Table S3). A single RCT reported postoperative DeMeester scores of adults who underwent robotic (n = 25) versus laparoscopic fundoplication (n = 25) and found no difference (Mean difference DeMeester Score = 1.60, 95%CI −0.25, 3.45) [63]. A single RCT was identified that reported 24 h pH monitoring comparison of adults who underwent robotic (n = 25) versus laparoscopic fundoplication (n = 25). Again, no difference was found (Mean difference % time = −1.05, 95%CI −2.71, 0.61) [58]. For postoperative PPI use, one RCT compared PPI use after robotic (n = 20) versus laparoscopic fundoplication (n = 20) and found that zero patients in the robotic group versus three patients in the laparoscopic group resumed PPI therapy within 12 months of their operation (RR = 0.14, 95%CI 0.01, 2.60) [59]. A single cohort study compared PPI use between 15 patients undergoing robotic fundoplication and 44 patients undergoing laparoscopic fundoplication [61]. At 4 years, 20% of patients undergoing robotic fundoplication reported regular PPI use compared to 25% of those who had undergone laparoscopic fundoplication (RR = 0.80, 95%CI 0.26, 2.60). Wrap failure was reported by one RCT [59] which reported no difference

Table 2 Cost comparison of robotic versus laparoscopic fundoplication

Per patient costs for robotic versus laparoscopic fundoplication			
Study	Robotic	Laparoscopic	Details of cost
Owen et al. [64]	10,644	7968	US dollars. Perioperative cost
Morino et al. [63]	3157	1527	EURO. Inpatient cost
Muller Stitch	3244	2743	EURO. Inpatient cost
Nakadi et al. [65]	27,561	5907	EURO. In hospital costs
Nakadi et al. [65]	26,088	936	EURO. Yearly investment and maintenance

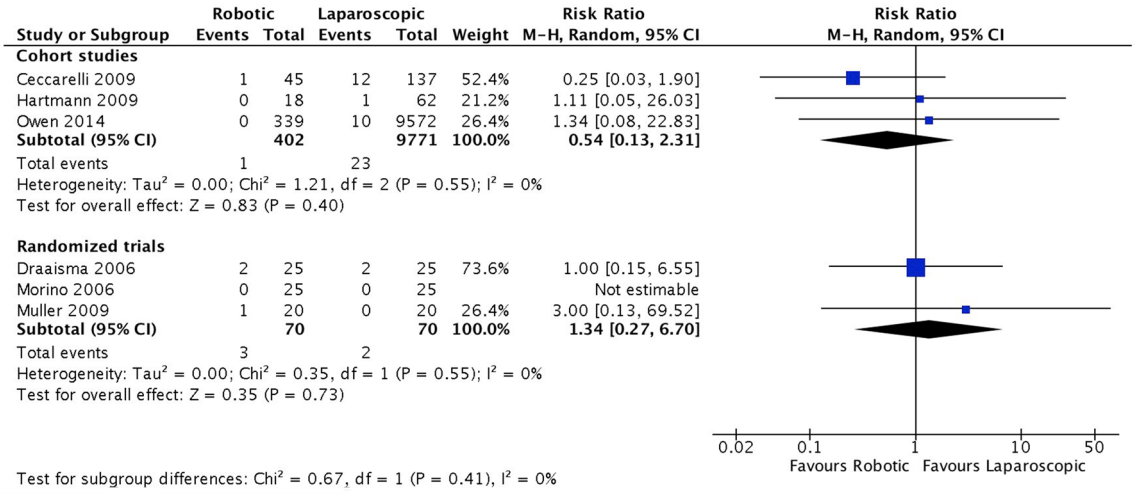

Fig. 12 Complications (Clavien-Dindo ≥ 3) laparoscopic compared to robotic fundoplication

in fundoplication wrap failure between robotic and laparoscopic fundoplication. One patient out of 20 patients randomized to robotic fundoplication experienced wrap failure, compared to zero of 20 patients randomized to laparoscopic fundoplication (RR = 3.00, 95%CI 0.13, 69.52). One cohort study reported a rate of zero wrap failures for both 45 robotic fundoplications and 137 laparoscopic fundoplications [60].

Pediatrics Symptom control: Three cohort studies compared symptom control in pediatric patients [66–68] (Fig. 13). Overall there was no difference between robotic ($n = 41$) and laparoscopic ($n = 41$) fundoplication for symptom control in these three studies (RR = 1.00, 95%CI 0.93, 1.07, $I^2 = 0\%$). There were no RCTs comparing symptom control between laparoscopic and robotic fundoplication in children.

Complications: Four cohort studies compared complications between robotic and laparoscopic fundoplication in children, with a total of 91 children undergoing robotic fundoplication and 91 undergoing laparoscopic fundoplication [66–69]. (Fig. 14) There were seven reported complications in the robotic group and eight complications reported in the laparoscopic group. There was no difference in complication rate between robotic and laparoscopic fundoplication (RR = 0.88, 95% CI 0.34, 2.23), though the risk ratio was only estimable from one study as no Clavien-Dindo > Grade 3 were reported in the other studies.

Postoperative length of stay: Three cohort studies compared mean length of stay for children undergoing robotic versus laparoscopic fundoplication, with no significant difference found (Mean difference in days = − 0.12, 95%CI − 1.25, 1.02, $I^2 = 37\%$) [67, 69, 70].

Remaining outcomes: We identified only single cohort studies comparing robotic and laparoscopic fundoplication in children for wrap failure, dysphagia, and cost (Supplemental Table S3). One cohort study compared wrap failure rate between robotic and laparoscopic fundoplication in children [67]. There were no wrap failures noted in children who underwent either robotic ($n = 25$) or laparoscopic ($n = 25$) fundoplication across a median follow-up time of 14 months (range 1–48 months). The same study found zero children in the robotic group that demonstrated postoperative dysphagia compared to one child in the laparoscopic group (RR = 0.33, 95%CI 0.01–7.81). For cost, Anderberg et al. found that robotic fundoplication was more expensive, 9582 Euros for robotic fundoplication versus 8982 Euros for laparoscopic fundoplication including in-hospital costs [70].

Key question 3

Risk of bias

A total of 43 studies met the inclusion criteria for KQ3 (complete versus partial fundoplication), which included 26

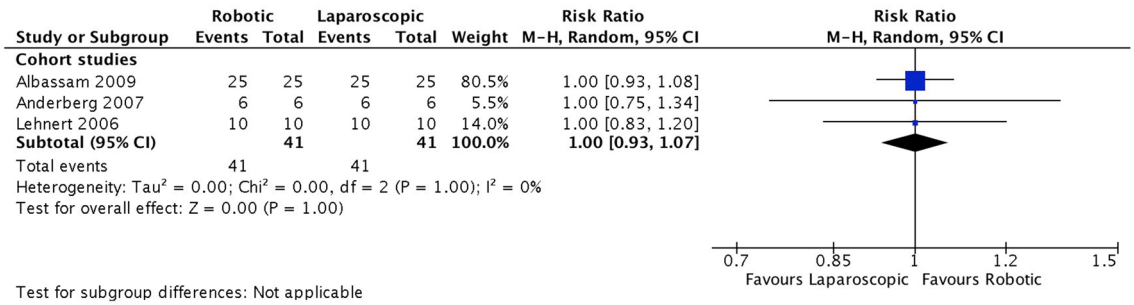

Fig. 13 Symptom control in pediatric patients laparoscopic compared to robotic fundoplication

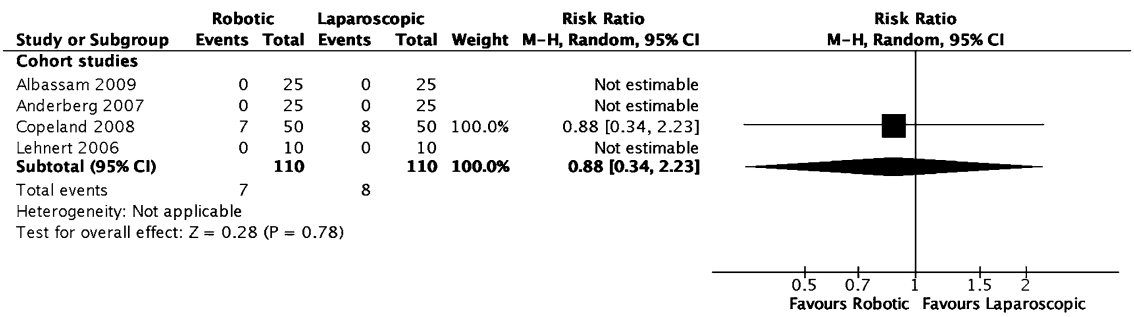

Fig. 14 Complications in pediatric patients for laparoscopic compared to robotic fundoplication

RCTs and 17 cohort studies. Risk of bias of included RCT and cohort studies are indicated in Supplemental Figure S7 and S8 respectively. Of the 26 RCTs, 20 were determined to have low overall bias (77%), four with high bias (15%), and two with unclear bias (8%). Four cohort studies were judged to have low risk of bias (24%), 12 with high risk of bias (71%), and one with unclear risk of bias (6%).

Adults Complications (Clavien-Dindo Grade 3–5): There were 11 RCT and 5 observational studies reporting on complications. Pooled analysis of RCT studies demonstrated no difference in complication rate between patients undergoing partial ($n=851$) versus complete ($n=834$) fundoplication (RR = 1.17, 95%CI 0.69, 2.01, $I^2=0\%$) [71–81]. (Fig. 15) Observational studies had a different pooled risk ratio, but still did not demonstrate any difference in complication rate between partial ($n=726$) and complete ($n=1585$) fundoplication [82–86]. A funnel plot is shown in Supplemental Figure S9 and does not suggest publication bias for RCTs; there were too few observational studies to make a similar judgement.

Long-term (> 5 years) dysphagia: Pooled analysis of four RCTs that reported on long-term dysphagia demonstrated lower risk of long-term dysphagia in patients undergoing partial ($n=196$) versus complete ($n=204$) fundoplication, however this effect did not reach statistical significance (RR = 0.73, 95%CI 0.52, 1.02, $I^2=0\%$) [19, 87–89]. (Fig. 16) Four observational studies also reported long-term dysphagia rates, and pooled analysis again demonstrated lower risk of long-term dysphagia in patients undergoing partial ($n=811$) versus complete ($n=904$) fundoplication [85, 90, 91].

Endoscopic dilation: Pooled analysis of neither randomized nor observational studies demonstrated statistically significant different rates of endoscopic dilation for patients undergoing partial versus complete fundoplication. In two randomized trials, 5 of 119 patients undergoing partial fundoplication required endoscopic dilation compared to 3 of 110 patients undergoing complete fundoplication (RR = 1.38, 95%CI 0.22, 8.61, $I^2=23\%$) [71, 79]. Five cohort studies including 1428 patients undergoing partial fundoplication and 2143 patients undergoing complete fundoplication showed a lower rate of endoscopic dilation in patients undergoing partial fundoplication, however there was both significant study heterogeneity and a wide confidence interval (RR = 0.69, 95%CI 0.20, 2.40, $I^2=67\%$) [84, 86, 92–94] (Fig. 17).

Reoperation: Fifteen RCTs compared wrap failure and reoperation rates in patients undergoing partial ($n=975$) versus complete ($n=961$) fundoplication, and pooled analysis indicated no significant difference (RR = 0.97, 95%CI 0.66, 1.45, $I^2=6\%$) [19, 72–79, 87, 89, 95–97]. (Fig. 18) Pooled analysis of nine observational studies reporting wrap failure and reoperation rates in patients undergoing partial

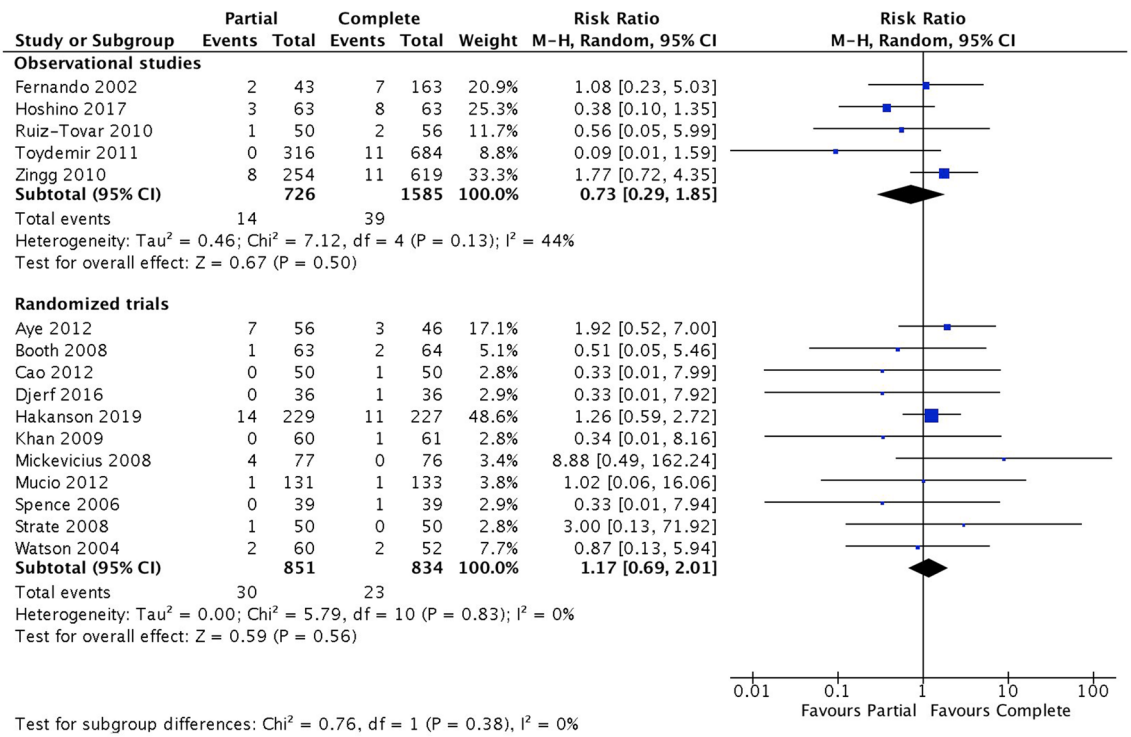

Fig. 15 Complications (Clavien-Dindo Grade 3–5) for complete compared to partial fundoplication

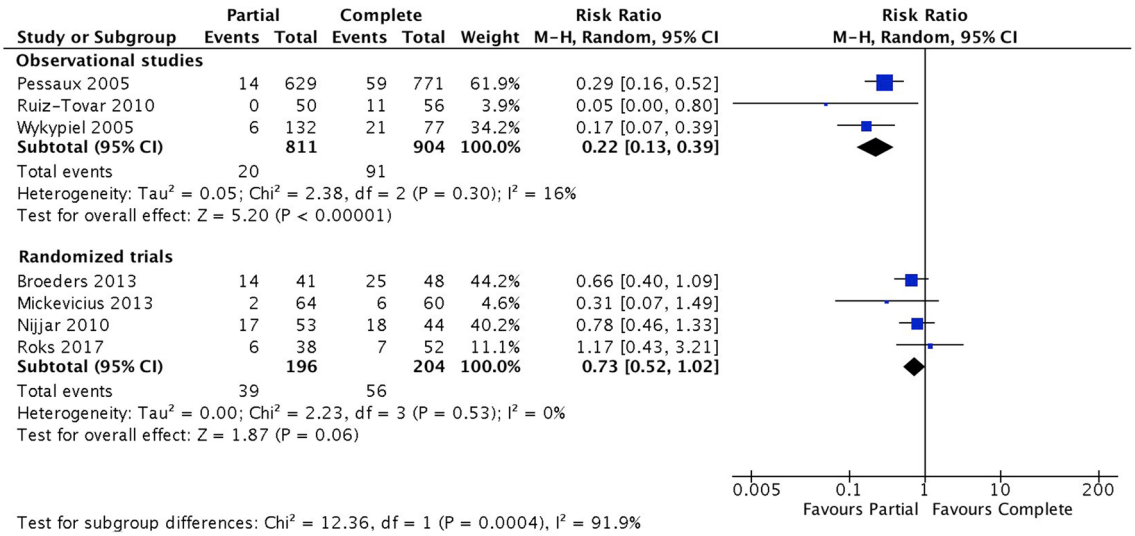

Fig. 16 Long-term (> 5 years) dysphagia for complete compared to partial fundoplication

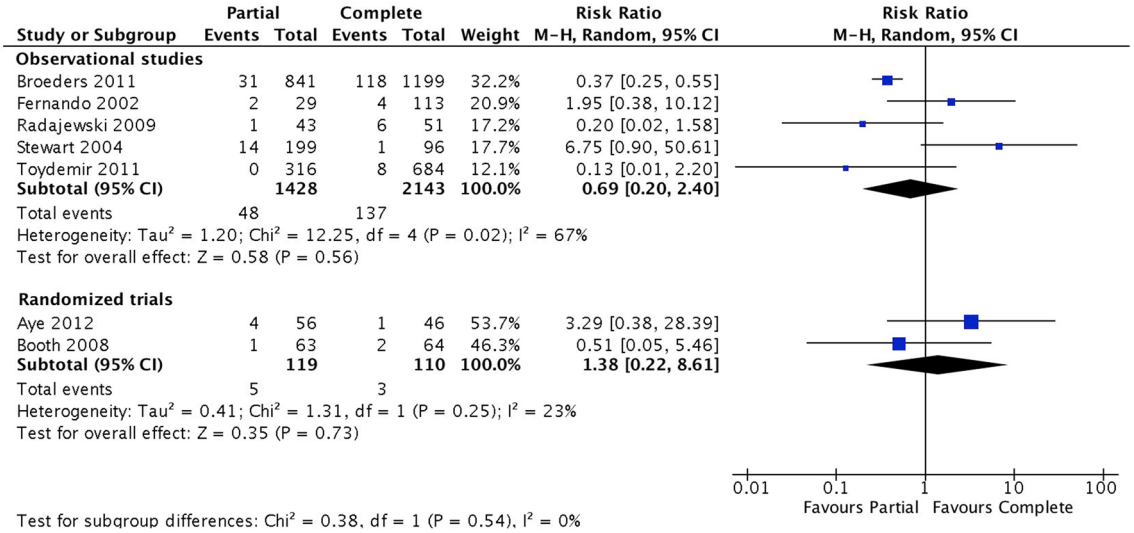

Fig. 17 Endoscopic dilation for complete compared to partial fundoplication

($n = 1975$) versus complete ($n = 2846$) fundoplication also demonstrated no statistically significant difference, though there was significant study heterogeneity (RR = 0.85, CI 0.35 to 2.05, $I^2 = 63\%$, $p = 0.005$) [82, 83, 85, 86, 92–94, 98, 99]. In Supplemental Figure S10, a funnel plot does not suggest publication bias for RCT's, and there were too few observational studies to definitively comment on observational studies.

Symptom control: Neither randomized nor observational studies demonstrated a statistically significant difference in rates of short-term symptom control between patients undergoing partial versus complete fundoplication for GERD. Nine RCTs including 502 patients undergoing partial fundoplication and 491 patients undergoing complete fundoplication were fairly heterogeneous, with pooled analysis finding no difference in symptom control between groups (RR = 0.96, 95%CI 0.90, 1.03, $I^2 = 47\%$, $p = 0.06$) [71, 75, 76, 79, 81, 87, 88, 100, 101]. Five observational studies demonstrated a similar point estimate, with pooled analysis again finding no difference in patients undergoing partial ($n = 614$) versus complete ($n = 957$) fundoplication [84, 86, 92, 94, 98]. (Fig. 19) A funnel plot in Supplemental Figure S11 does not strongly suggest publication bias for RCTs.

Long-term symptom control was also found to be similar between patients undergoing partial versus complete fundoplication in both randomized and observational studies.

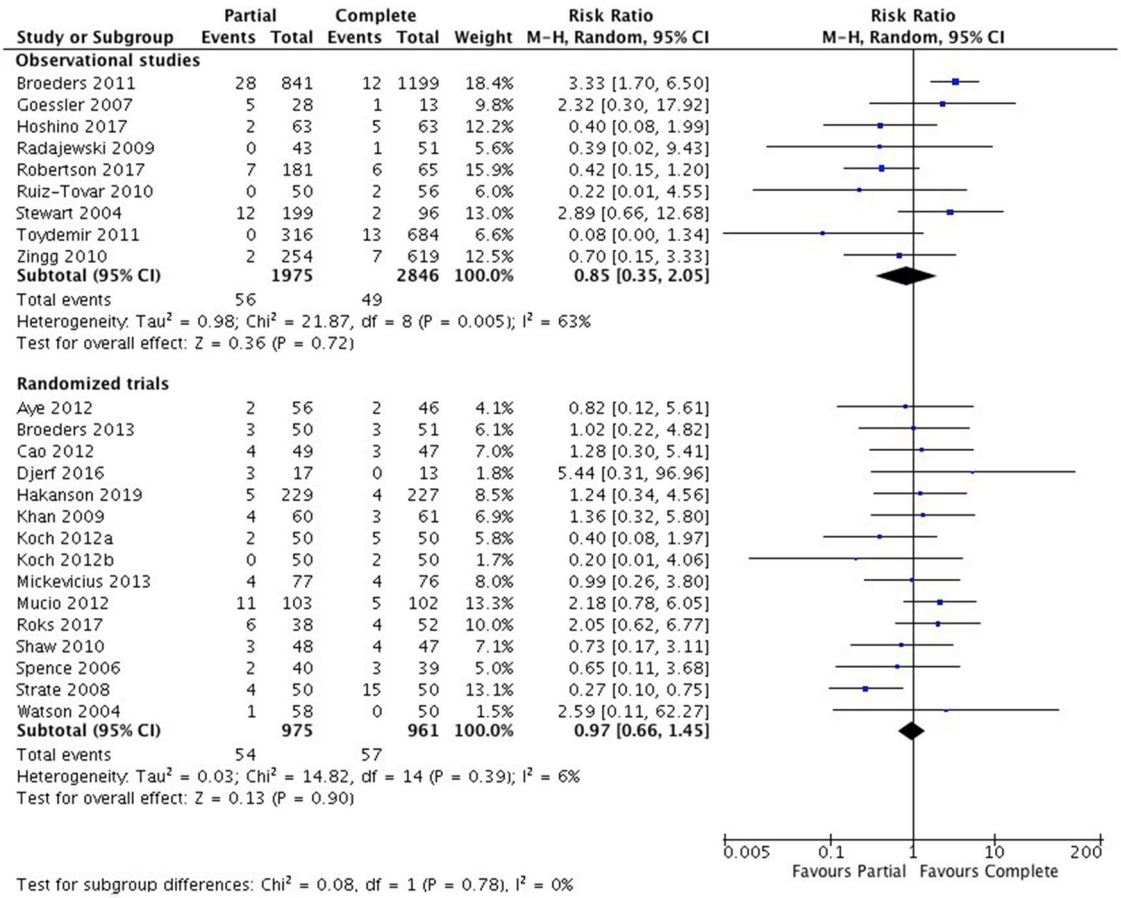

Fig. 18 Reoperation for complete compared to partial fundoplication

Six randomized studies comparing 408 patients undergoing partial fundoplication to 457 patients undergoing complete fundoplication found no statistically significant difference in the rate of symptom control, though there was near significant study heterogeneity (RR = 0.94, 95%CI 0.85, 1.04, $I^2 = 53\%$, $p = 0.06$) [19, 72, 87–89, 102]. (Fig. 20) Pooled analysis of observational studies also found no significant difference in long-term rates of symptom control [85, 90].

Prolonged PPI use: Seven randomized studies compared rates of long-term PPI use between patients undergoing partial ($n = 455$) versus complete ($n = 514$) fundoplication and found an increased use of prolonged PPI in patients undergoing partial fundoplication, however there was significant study heterogeneity and studies generally had high risk of bias (RR = 2.06, 95%CI 1.08, 3.94, $I^2 = 45\%$) [72, 73, 87–89, 102, 103]. Three observational studies including 234 patients undergoing partial fundoplication and 222 patients undergoing complete fundoplication found no significant difference in rates of prolonged PPI use between the two groups, though there was again significant study heterogeneity and high risk of bias (RR = 0.59, 95%CI 0.11, 3.23, $I^2 = 93\%$) [84, 85, 104]. (Fig. 21).

Quality of life: There was no difference in either short-term or long-term quality of life between patients randomized to undergo partial versus complete fundoplication (Figs. 22 and 23). For short-term QOL, five randomized studies compared 381 patients undergoing partial fundoplication to 373 patients undergoing complete fundoplication (SMD = 0.12, 95%CI − 0.02, 0.26, $I^2 = 0\%$) [73, 78, 79, 95, 100]. Long-term QOL was compared by five randomized studies including 390 patients undergoing partial fundoplication and 416 patients undergoing complete fundoplication and again found to have no difference, though there was substantial study heterogeneity (SMD = − 0.09, 95%CI − 0.38, 0.20, $I^2 = 73\%$) [19, 73, 74, 78, 89]. Observational data for short-term quality of life was pooled but comparison was not estimable; for long-term QOL [84, 92], two observational studies included 24 patients undergoing partial fundoplication and 81 patients undergoing complete fundoplication found no significant difference between groups [104, 105].

Remaining results: Additional outcomes comparing partial versus complete fundoplication are summarized in Supplemental Table S4. Pooled analysis of studies comparing pH normalization and DeMeester scores of patients

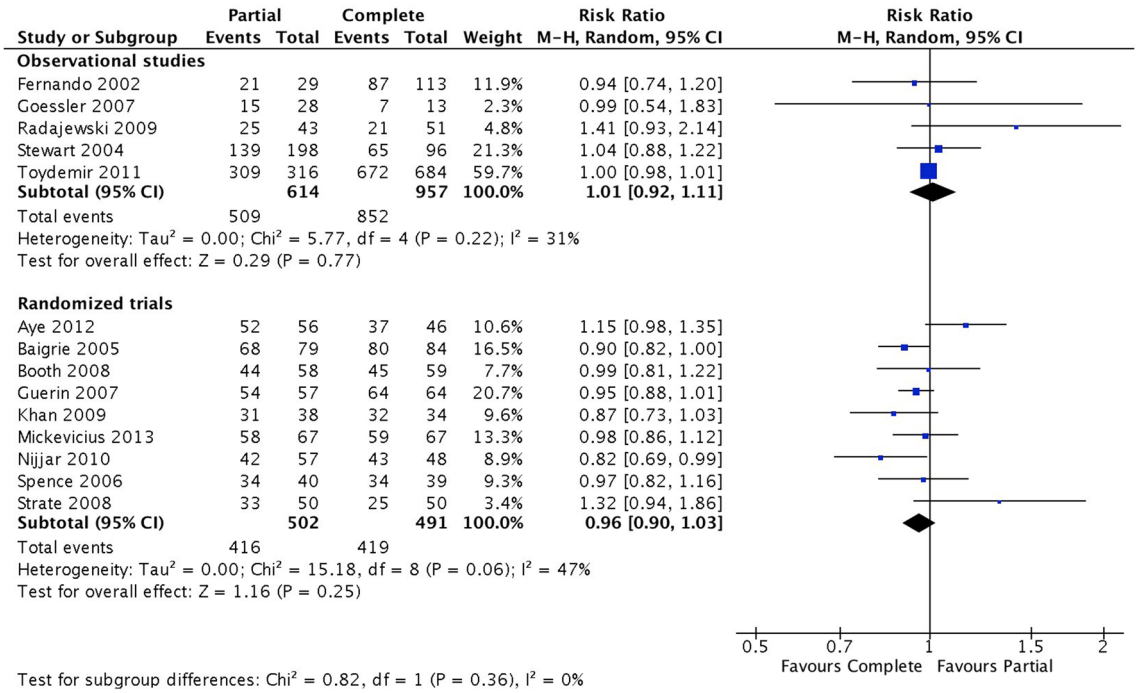

Fig. 19 Short-term (< 5 years) symptom control for complete compared to partial fundoplication

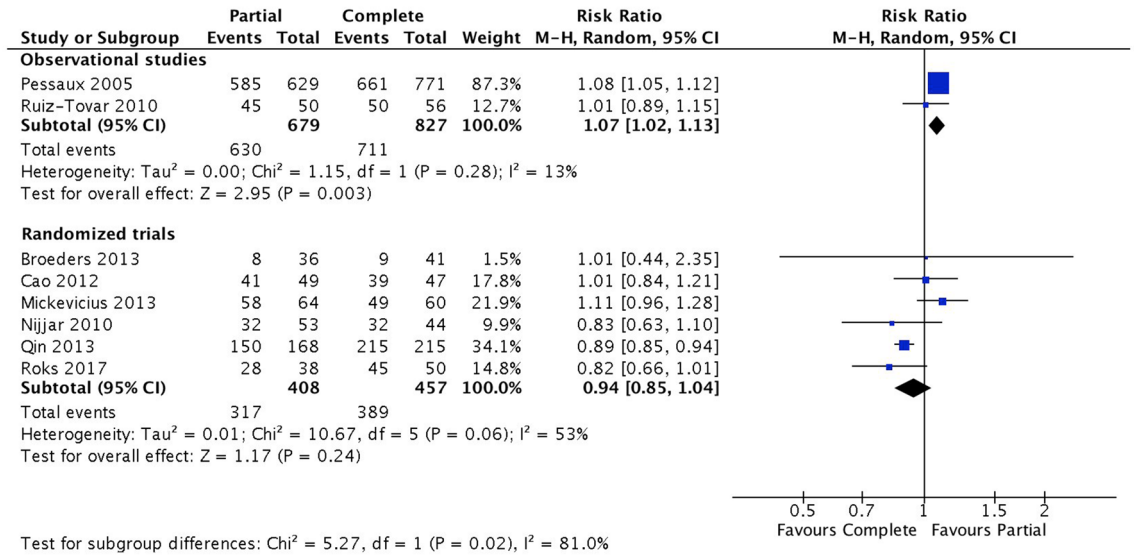

Fig. 20 Long-term (> 5 years) symptom control for complete compared to partial fundoplication

undergoing partial versus complete fundoplication showed no statistically significant difference. Six RCTs compared postoperative DeMeester scores between 398 patients undergoing partial fundoplication with 432 patients undergoing complete fundoplication (Mean difference = 1.39, 95%CI 0.97, 1.80, $I^2 = 0\%$) [72, 79, 95, 97, 102, 106]. Four RCTs compared pH normalization between patients undergoing partial fundoplication versus complete fundoplication and again showed no difference (Mean difference = − 0.23, 95%CI − 1.98, 1.53, $I^2 = 68\%$) [19, 73, 81, 97]. With regard to long-term gas bloat, randomized trials including 189 patients undergoing partial fundoplication and 197 patients undergoing complete fundoplication demonstrated no significant difference (RR = 0.96, 95%CI 0.77, 1.21, $I^2 = 9\%$) [19,

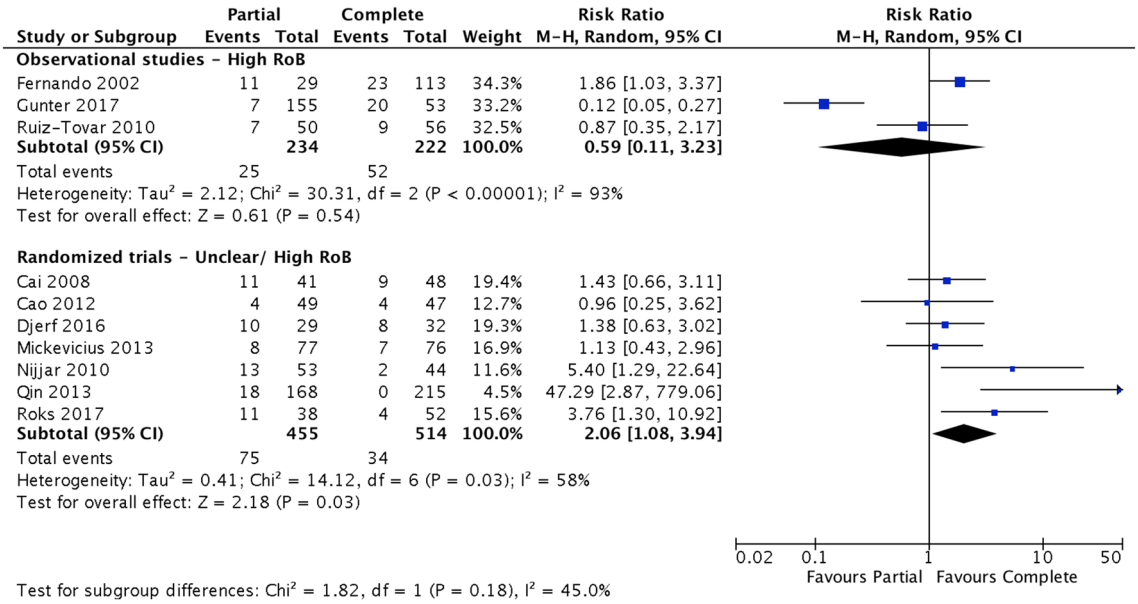

Fig. 21 Prolonged PPI use for complete compared to partial fundoplication

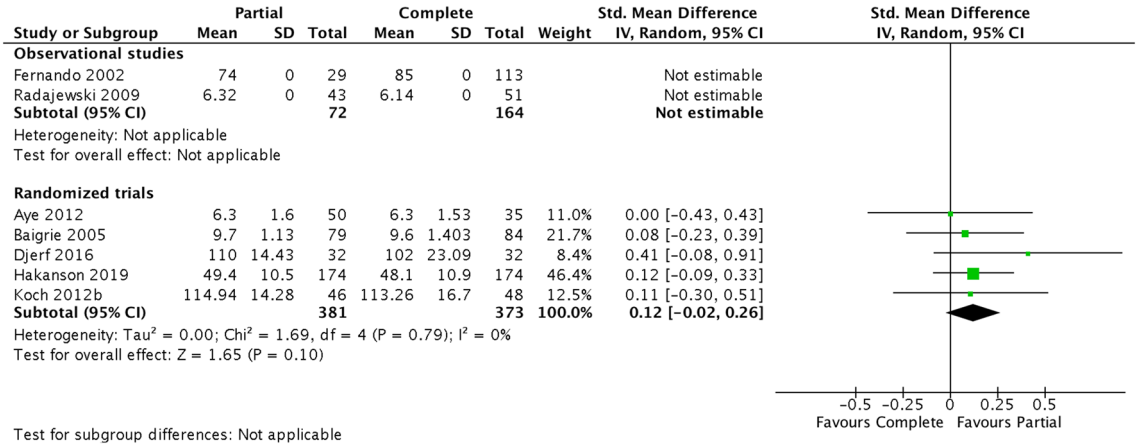

Fig. 22 Short-term (< 5 years) quality of life for complete compared to partial fundoplication

87–89]. Two high risk of bias observational studies demonstrated lower rates of gas bloat in patients undergoing partial fundoplication ($n = 761$) relative to patients undergoing complete fundoplication ($n = 848$), though there was substantial study heterogeneity (RR = 0.34, 95%CI 0.14, 0.84, $I^2 = 73\%$, $p = 0.06$) [90, 91].

Pediatrics Three pediatric studies compared outcomes between partial versus complete fundoplication. Two observational studies including 199 children undergoing partial fundoplication and 170 children undergoing complete fundoplication [107, 108]. One RCT included 82 children undergoing partial and 85 children undergoing complete fundoplication [109]. Outcomes of single studies and pooled analyses are reported in Supplemental Table S5. A single RCT found that children undergoing partial fundoplication have a statistically significant lower risk of requiring postoperative endoscopic dilation compared to children undergoing complete fundoplication (RR = 0.21, 95%CI 0.05, 0.92) [109]. On the other hand, there was a higher risk of wrap failure in children undergoing partial versus complete fundoplication (RR = 2.70, 95%CI 1.01, 7.22). Other outcomes were not found to be statistically significant between groups.

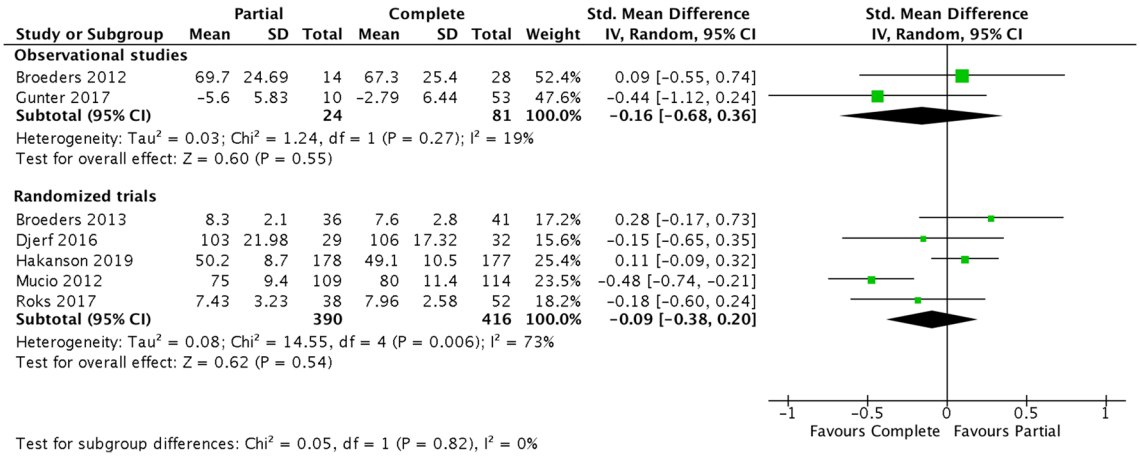

Fig. 23 Long-term (> 5 years) quality of life for complete compared to partial fundoplication

Key question 4

Risk of bias

A total of 13 studies met the inclusion criteria for KQ4 (division of short gastric vessels versus no division of short gastric vessels, minimal versus maximal dissection), which included 11 RCTs and two cohort studies. The risk of bias judgements for the RCTs are shown in Supplemental Figure S12. Five studies had low risk of bias (45%), five studies had high risk of bias (9%), and one study had an unclear risk of bias (45%). Two non-randomized studies were judged to have high risk of bias.

Division versus no division of short gastrics Long-term (> 5 year) symptom control: Two RCTs compared long-term symptom control between patients undergoing division or nondivision of the short gastric vessels during laparoscopic fundoplication, however, their effect estimates were opposite in direction. Kinsey-Trotman et al. followed 102 patients randomized to either division or non-division of short gastric vessels during laparoscopic Nissen fundoplication for 15–20 years, and found that fewer patients who did not have division of the short gastric vessels report heartburn (RR = 0.73, 95%CI 0.46, 1.14, high risk of bias) [20]. Mardani et al. followed 99 patients across 10 years, and found that patients who did not undergo division of the short gastric vessels had higher rates of heartburn (RR = 1.17, 95% CI 0.96, 1.42, low risk of bias) [110].

Short-term (< 5 years) symptom control: Six studies reported short-term symptom control (Fig. 24). Four of these studies were RCTs, with a total of 162 patients randomized to division of short gastric vessels and 170 patients randomized to no division. Overall there was no

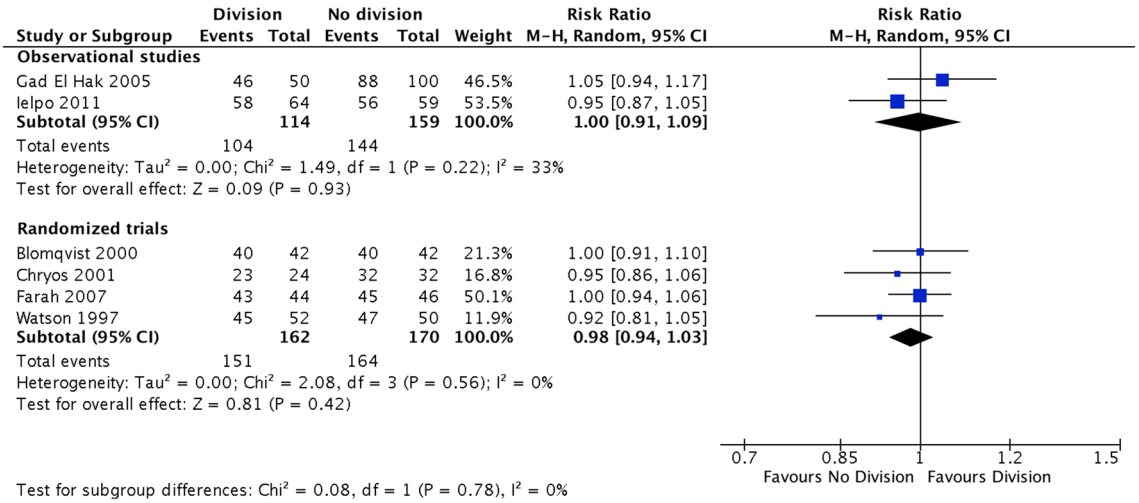

Fig. 24 Short-term (< 5 years) quality of life for division compared to no division on the short gastric vessels

difference in short-term symptom control between groups (RR = 0.98, 95%CI 0.94, 1.03, $I^2 = 0\%$) [111–114]. Two cohort studies with 114 patients undergoing division of short gastric vessels and 159 patients who did not undergo division of short gastric vessels also found no difference in symptom control [115, 116].

Esophageal acid: Three randomized studies compared esophageal acid exposure, which included DeMeester score and pH normalization, between adult patients undergoing division of short gastric vessels during laparoscopic fundoplication ($n = 98$) and those without division of short gastric vessels ($n = 98$) [111, 112, 117]. (Fig. 25) There was no difference in esophageal acid exposure as measured by DeMeester score (SMD = 0.15, 95%CI − 0.25, 0.56, $I^2 = 0\%$) or abnormal pH time (SMD = 0.18, 95%CI − 0.22, 0.57).

Long-term (> 5 years) dysphagia: Three RCTs measured long-term dysphagia in adult patients undergoing division of short gastric vessels ($n = 94$) or no division of short gastric vessels ($n = 98$) during laparoscopic fundoplication [20, 110, 117]. (Fig. 26) Overall, there was no difference in rates of long-term dysphagia between groups (RR = 0.97, 95%CI 0.66, 1.42, $I^2 = 0\%$). Long-term dysphagia was reported in 27 of 94 (29%) patients undergoing division of short gastric vessels versus 32 of 98 (33%) patients who underwent laparoscopic fundoplication without division of short gastric vessels.

Surgical complications (Clavien-Dindo grade 3–5): Four RCTs compared surgical complication rates for patients undergoing laparoscopic fundoplication with ($n = 172$) or without ($n = 175$) division of short gastric vessels [111–114]. (Fig. 27) There was no difference in complication rates between groups (RR = 2.05, 95%CI 0.59, 7.15, $I^2 = 0\%$). The two cohort studies also did not find any difference in complication rates when patients did or did not undergo division of short gastric vessels during laparoscopic fundoplication [115, 116].

Endoscopic dilation: Two RCTs compared rates of endoscopic dilation in patients undergoing division ($n = 94$) or nondivision ($n = 95$) of short gastric vessels during laparoscopic fundoplication [113, 118]. (Fig. 28) There was no difference in rates of endoscopic dilation between the two patient groups (RR = 1.22, 95%CI 0.37, 4.02, $I^2 = 0\%$). Rates of endoscopic dilation were also not different between groups in the one cohort study that reported this outcome [116].

Long-term (> 5 years) quality of life: Three RCTs reported on long-term quality of life using two different scales [20, 110, 117]. The GI QOL from two studies had a SMD of 0 (95% CI − 0.38 to 0.37, $I^2 = 0\%$), while the third

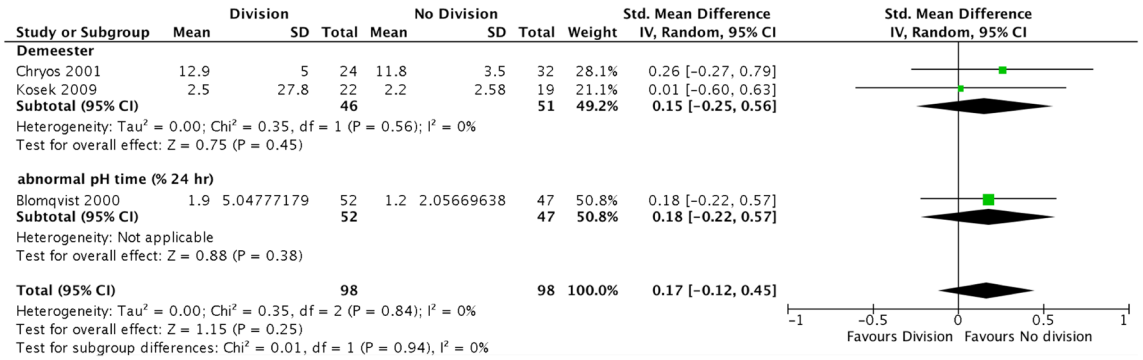

Fig. 25 Esophageal acid for division compared to no division on the short gastric vessels

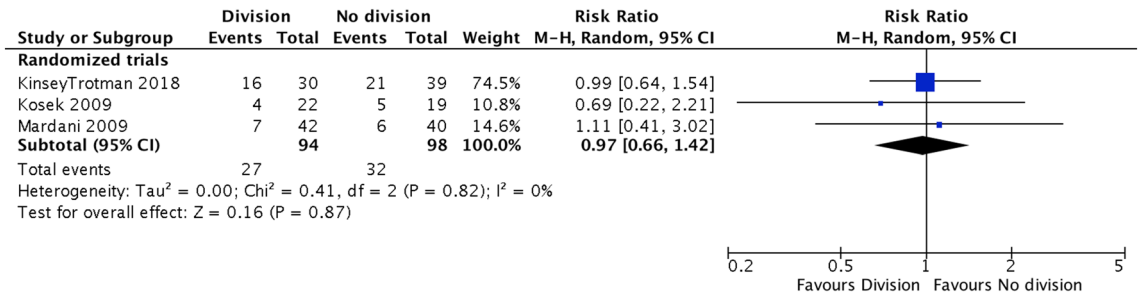

Fig. 26 Long-term (> 5 years) dysphagia for division compared to no division on the short gastric vessels

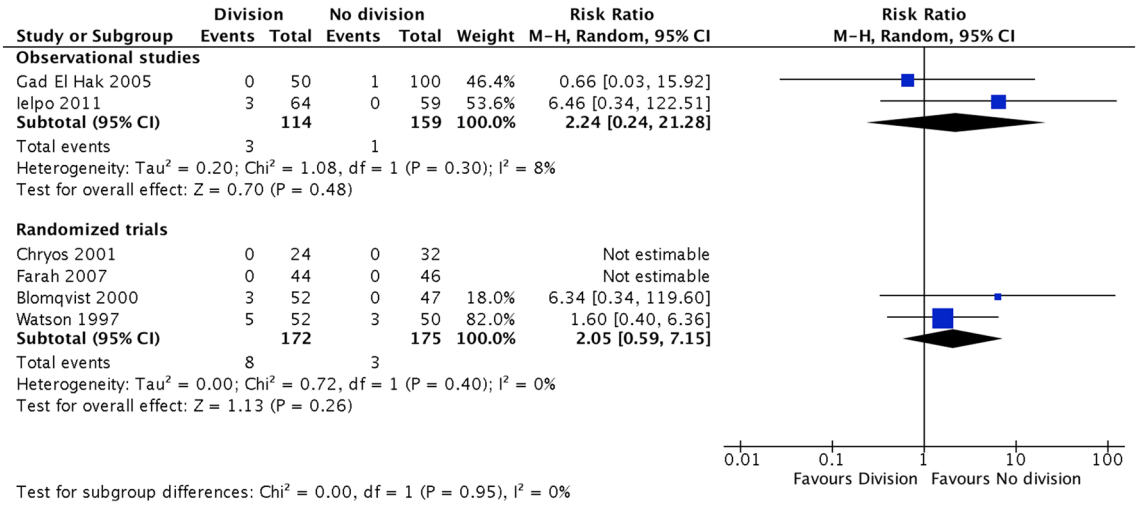

Fig. 27 Surgical complications (Clavien-Dindo grade 3–5) for division compared to no division on the short gastric vessels

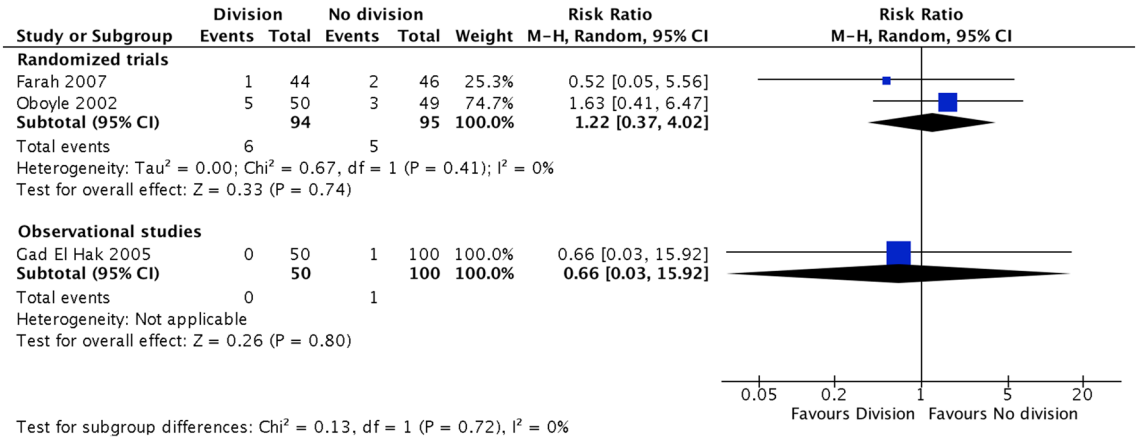

Fig. 28 Endoscopic dilation for division compared to no division on the short gastric vessels

study [110] reported on general QOL (scale max = 110) and demonstrated slightly higher quality of life in patients who had undergone division of the short gastric vessels (Mean difference = 1.6, 95%CI 1.1, 2.1).

Remaining outcomes: Several outcomes were reported by two or fewer RCTs. Two RCTs compared long-term gas bloat symptoms between patients undergoing division of short gastric vessels versus patients who did not undergo division of these vessels and found no difference (RR = 1.41, 95%CI 0.77, 2.61, $I^2 = 72\%$) [20, 110]. Postoperative PPI use was compared by two RCTs and found to be no different between patients undergoing division of short gastric vessels compared to those who did not undergo division (RR = 0.73, 95%CI 0.36, 1.47, $I^2 = 0\%$) [20, 110].

Only one high risk of bias observational study [116] reported on wrap failure, as defined by reoperation due to symptom recurrence with a very wide confidence interval, demonstrated only three events in 150 patients (RR = 4.13, 95%CI 0.36, 46.63).

Minimal versus maximal dissection Two studies compared the outcomes of minimal versus maximal dissection during laparoscopic fundoplication in children, either in an observational or prospective, randomized fashion. There was one study addressing esophageal minimal (MIN) versus maximal (MAX) dissection for children undergoing laparoscopic fundoplication (MIN $n = 90$, MAX $n = 87$) [119]. The reoperation rate was significantly higher in the maximal dissection group (MIN 3.3% vs MAX 18.4%, RR = 0.21, 95%CI 0.06, 0.67, $p = 0.006$) (Table 3). A second study with longer follow-up supports the original findings but there was a greater than 50% attrition rate [120].

Table 3 Outcomes for minimal versus maximal dissection during laparoscopic fundoplication in children

Outcome	Minimal dissection, no. (%)	Maximal dissection, no. (%)	Risk ratio (95% CI)
Weight gain	84/90 (83.3%)	75/87 (96.6%)	1.08 (0.98, 1.20)
Reoperation for symptom recurrence	3/90 (3.3%)	16/87 (18.4%)	0.21 (0.06, 0.67)*
Endoscopic dilation	0/90 (0%)	6/87 (6.9%)	0.08 (0.00, 1.46)
Readmission or respiratory reason	11/90	15/87	0.71 (0.35, 1.46)

*$p = 0.006$

Discussion

GERD is a very common and morbid medical condition affecting millions of individuals worldwide. Both medical and surgical treatment options are available and effective for the management of GERD. The purpose of this systematic review was to review the literature and pool data when possible to better inform decisions for the surgical care for patients suffering from GERD.

Summary of evidence

When comparing medical and surgical treatment of GERD, we found that only a minority of comparative cohort or randomized control trials had a low risk of bias. With this limitation in mind, our systematic review and meta-analysis demonstrated that patients undergoing surgical treatment of GERD had superior short-term, but not long-term (> 5 years follow-up), quality of life relative to patients treated medically with PPIs. Patients undergoing surgery also demonstrated better short-term and long-term symptom control as well as evidence of improved pH normalization relative to medically treated patients. As expected, patients treated medically did demonstrate higher rates of long-term PPI usage, yet 28% of patients who underwent operative treatment of GERD also were using PPI on follow-up, raising questions of whether their surgery had been ineffective or if they were prescribed PPIs for other reasons [121, 122]. Surgically treated patients also had slightly higher complication rates, though when pooling data from only low risk of bias studies, there was no difference in complication rates. Data comparing medical and surgical therapy in pediatric patients was extremely limited with no comparative studies identified in our search.

In regard to comparison of minimally invasive techniques (robotic versus laparoscopic fundoplication), our systematic review identified only a handful of comparative studies with low risk of bias. On pooled analysis for symptom control, complications, and length of stay there was no significant difference between outcomes for patients undergoing robotic versus laparoscopic fundoplication. The cost of robotic fundoplication was higher than laparoscopic fundoplication in identified studies. Again, the comparative literature in the pediatric population was extremely limited, though available data did not demonstrate any difference in complications or postoperative length of stay on pooled analysis.

The literature search for comparative studies on complete versus partial fundoplication yielded the highest number of high-quality papers, with 20 of 26 RCTs judged to have a low risk of bias. On pooled analysis, patients undergoing partial fundoplication had a lower risk of long-term dysphagia than patients undergoing complete fundoplication. There was no difference between the groups in complication rate, rates of endoscopic dilation, reoperation rate, short or long-term symptom control, short or long-term quality of life, and postoperative measures of pH normalization including DeMeester scores. Prolonged PPI use was noted to be higher in patients undergoing partial fundoplication, though there was high study heterogeneity and risk of bias in these data. Pediatric comparative data, essentially limited to a single RCT, demonstrated that children undergoing complete fundoplication had a higher risk of requiring endoscopic dilation but were also had a lower rate of wrap failure.

Finally, we reviewed the literature comparing outcomes of adult patients undergoing division of short gastric vessels versus no division of short gastric vessels and pediatric patients undergoing minimal versus maximal dissection during fundoplication. On pooled analysis, there was no difference in patient outcomes for short or long-term symptom control, esophageal acid exposure, long-term dysphagia, surgical complications, and rates of endoscopic dilation. For pediatric patients, one study comparing minimal versus maximal dissection demonstrated higher rates of reoperation for children undergoing maximal dissection [119].

Relationship to literature

Our systematic review results are comparable to existing systematic reviews examining similar research questions. A 2015 Cochrane review comparing medical versus surgical treatment for GERD using only RCTs also found that patients undergoing surgery reported improved short-term quality of life and symptom control although patients undergoing surgery also manifested higher rates of dysphagia [123]. A 2014 systematic review comparing medical and surgical treatment of GERD also noted improved short-term

symptom control in patients undergoing antireflux surgery, but similar to our results, found that a portion of surgical patients continue PPI therapy even after undergoing surgical treatment of GERD [124]. As in our study, the results for both these systematic reviews were limited by low study quality and heterogeneity of outcome measurements. A recent 2020 systematic review examined outcomes of partial versus complete fundoplication in adult patients and similarly reported increased rates of dysphagia in patients undergoing complete fundoplication relative to patients undergoing partial fundoplication [125]. Systematic reviews in the pediatric surgery literature also mirror our results, with very little high quality evidence for pediatric outcomes both when comparing medical management to surgical intervention and partial versus complete fundoplication [126, 127]. The current systematic review updates the literature search from prior reviews, and incorporates multiple treatment questions into a single reference document for surgeons engaged in the treatment of GERD.

Limitations

Study results are limited by a number of factors. First, few included studies were found to have low risk of bias when judged using the Cochrane risk of bias tool and the Newcastle Ottawa Scale. Included studies often demonstrated weaknesses including low patient numbers as well as frequent imprecision and indirectness of outcome reporting. Additionally, few outcomes were reported as objective measures, such as DeMeester score and pH normalization. Instead, many of the reported outcomes relied on heterogeneous and/or subjective instruments, such as quality of life or symptom control. Differences in quality of life and definitions of symptom control contribute to imprecision of outcome reporting and challenges in completing meaningful pooled analysis. These limitations are presented transparently and taken in consideration by separating high risk and low risk of bias studies in all analysis.

It is also important to note that many of the included studies were from earlier eras of surgical therapy, possibly reflecting outcomes associated with the learning curve of robotic and laparoscopic procedures and not current outcome patterns. For example, in one paper comparing the outcomes of patients undergoing division of short gastric vessels versus no division of short gastric vessels, the operative time was reported to be 40 min longer when patients underwent division of short gastric vessels [116], suggesting that the study surgeons may still have been in their learning curve of laparoscopic fundoplication. Many of the trials with the longest follow up have patient populations who underwent laparoscopic fundoplication over 15 years ago [19, 20, 89], and thus those patient outcomes may not accurately represent the outcomes of patients undergoing laparoscopic anti-reflux procedures in the present day. Trials comparing robotic versus laparoscopic fundoplication from over 10 years ago may also represent earlier robotic experiences that are not necessarily representative of current outcomes [59–62]. One additional limitation to note is that patients undergoing operative intervention in the included studies often receive treatment at highly specialized centers, and as such their outcomes may not be generalizable to patients undergoing anti-reflux procedures in different settings.

In addition to limitations inherent to the included studies, it is also important to note limitations of the systematic review process itself. It is possible that our search terms did not include all relevant comparative studies, although we reviewed reference lists of included studies in order to further identify relevant studies that were not captured by our search terms. Another way we attempted to ensure an adequate search was to employ the assistance of a librarian. Furthermore, our exclusion criteria included outcomes reported in single arm studies or cohort studies with smaller numbers of patients in case RCT data was limited. Finally, we a priori defined long-term outcomes as > 5 years. This definition of long-term outcomes excluded many studies with shorter term follow-up from contributing to analyses, given the lack of studies had with > 5-year follow-up.

Relevance to clinical practice

The overall findings of this systematic review highlight the importance of informed consent and patient counseling when treating GERD. For example, with regard to medical or surgical treatment of GERD, patients should be counseled of the relative risks and benefits of undergoing operative intervention for GERD. For some patients, the potential benefit of PPI discontinuation and improved symptom control are worth the increased cost and potentially higher complication rate. For complete versus partial fundoplication, surgeons may highlight the potential increased risk for dysphagia with complete fundoplication and critically address patient preferences and tradeoffs with regard to PPI usage versus dysphagia. For specific surgical approaches, robotic fundoplication was found to be equivalent to laparoscopic fundoplication but more expensive. In the pediatric population, the evidence suggests minimal dissection during fundoplication is associated with lower re-operative rates relative to maximal dissection. The findings of this systematic review may not be directly translatable to populations such as patients with esophageal motility disorders or Barrett's esophagus, and may also not be pertinent to patients being evaluated for re-operative anti-reflux surgery.

Future research recommendations

This systematic review highlights the relative paucity of high-quality data with regard to surgical treatment of GERD. We found that many comparative studies suffer from high risk of bias, limiting the strength of conclusions, though a few examples of high quality, low risk of bias studies exist [17, 59, 77, 110]. Double-blind, placebo controlled randomized control trials are considered the gold standard of clinical trial design, and yet in surgery RCTs account for only a small fraction of publications [128, 129]. Challenges to successfully completing surgical RCTs include the presence of genuine clinical equipoise, difficulty in assessing endpoints, and small target populations. In addition, other unaccounted surgeon factor variables such as the heterogeneity of surgeon skill, different surgical technique used, as well as surgeon learning curves contribute to difficulty in comparing arms [129]. With regard to GERD, we encountered many of these challenges. Future studies would benefit from better defined endpoints such as symptom control and quality of life and studies using multiple surgeons that are past their learning curves. The challenges of surgical RCTs are further amplified in pediatric populations, contributing to an even greater dearth of high-quality pediatric data. Large database analyses may offer complementary information to RCTs addressing the surgical treatment of GERD by describing population level outcomes of large groups of patients across practice environments. At the same time, database research also has its own set of limitations including retrospective review and database granularity and quality.

Conclusion

Available evidence indicates that anti-reflux surgery offers superior short-term symptom control and higher quality of life than medical treatment of GERD, with the caveat that a proportion of patients undergoing operative treatment of GERD continue PPI treatment. Robotic fundoplication was equivalent to laparoscopic fundoplication but costlier. Further, complete fundoplication leads to higher postoperative dysphagia compared with partial fundoplication with no significant difference in rates of patient reported symptom control. However, partial fundoplication was associated with higher rates of PPI usage compared to complete fundoplication. There were higher reoperation rates for children undergoing fundoplication with maximal dissection versus minimal dissection. High quality randomized comparative studies or population-based studies may inform future understanding of the optimal surgical management of GERD. The results of this review and meta-analysis will be used to inform upcoming clinical practice guidelines.

Appendix 1

See Table 4.

Table 4 KQ1 embase search strategy

Gastroesophageal reflux'/mj AND ('antireflux operation'/mj OR 'antireflux operation' OR 'antireflux procedure' OR 'antireflux surgery') AND ('therapy'/mj OR 'combination therapy' OR 'disease therapy' OR 'disease treatment' OR 'diseases treatment' OR 'disorder treatment' OR 'disorders treatment' OR 'efficacy, therapeutic' OR 'illness treatment' OR 'medical therapy' OR 'medical treatment' OR 'multiple therapy' OR 'polytherapy' OR 'somatotherapy' OR 'therapeutic action' OR 'therapeutic efficacy' OR 'therapeutic trial' OR 'therapeutic trials' OR 'therapeutics' OR 'therapy' OR 'therapy, medical' OR 'treatment effectiveness' OR 'treatment efficacy' OR 'treatment, medical')

AND

(2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim)

Plus

Gastroesophageal reflux'/mj AND ('antireflux operation'/mj OR 'antireflux operation' OR 'antireflux procedure' OR 'antireflux surgery') AND ('therapy'/mj OR 'combination therapy' OR 'disease therapy' OR 'disease treatment' OR 'diseases treatment' OR 'disorder treatment' OR 'disorders treatment' OR 'efficacy, therapeutic' OR 'illness treatment' OR 'medical therapy' OR 'medical treatment' OR 'multiple therapy' OR 'polytherapy' OR 'somatotherapy' OR 'therapeutic action' OR 'therapeutic efficacy' OR 'therapeutic trial' OR 'therapeutic trials' OR 'therapeutics' OR 'therapy' OR 'therapy, medical' OR 'treatment effectiveness' OR 'treatment efficacy' OR 'treatment, medical')

AND

Gastroesophageal reflux'/de AND (2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)

Plus

('Barrett esophagus'/mj OR 'barrett esophagus' OR 'esophagus ulceration, barrett') AND ('antireflux operation'/mj OR 'antireflux operation' OR 'antireflux procedure' OR 'antireflux surgery') AND ('therapy'/mj OR 'combination therapy' OR 'disease therapy' OR 'disease treatment' OR 'diseases treatment' OR 'disorder treatment' OR 'disorders treatment' OR 'efficacy, therapeutic' OR 'illness treatment' OR 'medical therapy' OR 'medical treatment' OR 'multiple therapy' OR 'polytherapy' OR 'somatotherapy' OR 'therapeutic action' OR 'therapeutic efficacy' OR 'therapeutic trial' OR 'therapeutic trials' OR 'therapeutics' OR 'therapy' OR 'therapy, medical' OR 'treatment effectiveness' OR 'treatment efficacy' OR 'treatment, medical')

AND

Barrett esophagus'/de AND (2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim)

Plus

('Barrett esophagus'/mj OR 'barrett esophagus' OR 'esophagus ulceration, barrett') AND ('antireflux operation'/mj OR 'antireflux operation' OR 'antireflux procedure' OR 'antireflux surgery') AND ('therapy'/mj OR 'combination therapy' OR 'disease therapy' OR 'disease treatment' OR 'diseases treatment' OR 'disorder treatment' OR 'disorders treatment' OR 'efficacy, therapeutic' OR 'illness treatment' OR 'medical therapy' OR 'medical treatment' OR 'multiple therapy' OR 'polytherapy' OR 'somatotherapy' OR 'therapeutic action' OR 'therapeutic efficacy' OR 'therapeutic trial' OR 'therapeutic trials' OR 'therapeutics' OR 'therapy' OR 'therapy, medical' OR 'treatment effectiveness' OR 'treatment efficacy' OR 'treatment, medical' OR 'proton pump inhibitor'/mj OR 'gastric proton pump inhibitor' OR 'hydrogen potassium adenosine triphosphatase inhibitor' OR 'hydrogen potassium atpase inhibitor' OR 'proton pump inhibitor' OR 'proton pump inhibitors')

AND

Barrett esophagus'/de AND (2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND 'proton pump inhibitor'/de

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Declarations

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