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Looking back on a gold standard: a systematic literature review of laparoscopic Nissen fundoplication as an anti-reflux treatment option

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Summary
Background Laparoscopic Nissen fundoplication is considered the gold standard in surgical management of gastroesophageal reflux disease. Therefore, exhaustive scrutiny of the procedure is necessary. The aim of this study was to perform a complete and systematic literature review of laparoscopic Nissen fundoplication to summarize the evidence for safety and efficacy over time.
Methods MEDLINE, Embase, CINAHL, the Cochrane Library, and Web of Science were searched for randomized controlled trials investigating intra- and postoperative outcomes at follow-ups between 4–6 weeks and 17 years.
Results Among 1675 screened articles, 63 articles were identified comprising 40 trials with a total of 2619 participants. Intraoperative events included bleeding (2.9%), gastroesophageal injury/perforation (0.9%), and spleen injury/splenectomy (0.9%). One-year clinical follow-up presented the following: dysphagia (22.4%), heartburn or epigastric/sternal pain (15.1%), gas bloating (30.1%), and inability to vomit/belch (16.4%). These outcomes displayed a U-shaped curve with a minimum of symptoms at 1 year. At 10 years postoperatively, clinical outcomes deteriorated, demonstrating dysphagia (45.3%), heartburn or epigastric/sternal pain (30.9%), inability to vomit/belch (48.8%), and gas bloating (44.4%). Furthermore, the surgical benefit seems to dissipate at 17 years. At 1 and 10 years after surgery, reoperation rates were 6.7% and 16.3%, whereas proton pump inhibitor (PPI) use was at 12.3% and 23.3%, respectively.
Conclusion The performance of Nissen fundoplication declines over time, as demonstrated by increased PPI medication usage for recurrent symptoms and an increased reoperation rate reaching a combined 39.6%, representing failures after 10 years. The complication rates are dominated by dysphagia, gas bloating, inability to belch/vomit, and/or recurrent reflux symptoms with heartburn.

Keywords LNF · Laparoscopic surgery · Anti-reflux surgery · Gastroesophageal reflux · Systematic review

Main novel aspects

1. This review of laparoscopic Nissen fundoplication (LNF) is the first to cover 63 articles representing 40 different randomized trials including 2619 patients and synthesizing both intra- and postoperative endpoints using specific follow-up timepoints to showcase the safety and performance of LNF from both a short- and long-term perspective, unlike previous reviews, which have generally combined different timepoints into postoperative follow-up.
2. Publications based on single studies and especially retrospective studies often have lower-quality data and more missing patients compared to randomized

Johanna Hoffsten and Shuchesmita Das are no longer at the Karolinska Institutet, although this is the institution at which they conducted most of the study.

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studies, where both the financial resources and study efforts are higher. Therefore, a systematic review of only randomized articles increases the strength of the data.

3. By scrutinizing the evidence from trials published over the past 25 years, this review was able to show that the performance of LNF declines over time, as shown by increased use of proton pump inhibitor (PPI) medication to manage recurrent symptoms and the increased complication rate leading to more reoperations. Furthermore, this review showcased that dysphagia and recurrent reflux symptoms seem to be the main causes of reoperation with LNF. In addition, it also became apparent that clinical outcomes deteriorate 10 years postoperatively and that the surgical benefit of LNF seems to dissipate at 17 years.

Introduction

Gastroesophageal reflux disease (GERD) results from reflux of gastric content into the esophagus, which may cause troublesome symptoms or complications [1]. Heartburn and regurgitation are typical symptoms of GERD, with esophagitis and Barrett's esophagus as potential complications that develop over time [1]. Although there is regional variation in prevalence, GERD is a common condition worldwide, with more than a billion cases [2]. Furthermore, there are indications that the global burden is increasing [2].

Available treatment strategies include a spectrum of interventions such as lifestyle modifications, medical therapy, and anti-reflux surgery [1]. Indications for surgical treatment include persistent symptoms despite optimally dosed medical therapy or reluctance regarding long-term medication use [1]. Anti-reflux surgery comprises several techniques, but the current standard is laparoscopic fundoplication [3]. The most frequently employed technique, which is considered the gold standard, is laparoscopic Nissen fundoplication (LNF) [1, 3]. This involves a complete (360°) fundal wrap around the lower esophageal sphincter (LES) and, unsurprisingly, it is extensively reported in the literature [4–10].

LNF is generally viewed as a safe and effective treatment method for patients with GERD, although it is, as is any other procedure, associated with certain complications and side effects [3]. Furthermore, the evidence is inconclusive despite the plethora of literature on the matter [4–10]. To circumvent the disadvantages associated with LNF, other surgical options have been developed, such as the Toupet fundoplication technique that utilizes a more reserved 270° fundal wrap [3–7, 9, 10]. However, these alternatives have their own challenges in terms of balancing the respective benefits and harms, resulting in LNF's maintained popularity [4–6, 8–10].

Amidst the wide range of published literature on LNF, questions remain regarding the effectiveness of the technique and the need for exhaustive scrutiny of the procedure that collates the available empirical evidence.

Objective

The aim of this study was to perform a systematic literature review to summarize the evidence regarding the long-term postoperative safety and performance of LNF in adults with GERD.

Methods

This systematic literature review was conducted by including elements of the review process outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. The protocol was registered at www.researchregistry.com (Identification number: Reviewregistry1176). In this review, only data pertaining to LNF are presented, without any comparator treatment modalities. Since LNF is currently the most often conducted anti-reflux procedure globally, the purpose of this style of presentation is to enrich clinical knowledge with a specific focus on LNF safety and efficacy. Furthermore, although there are several systematic literature reviews that focus on LNF, the included studies in these reviews are not recent (i.e., not from within the past 10 years), and the additional information provided in our review may confirm or provide additional context based on the latest evidence.

Eligibility criteria

- Study design: randomized controlled trial (RCT).
- Participants: adults diagnosed with GERD.
- Intervention: LNF to treat GERD.
- Comparator: other surgical procedures, such as variations of LNF and open surgery, and medication for management of GERD.
- Follow-up periods: short-term follow-up of 1 month, 6 weeks, and 6 months. Long-term follow-up of 1 year, 5 years, and ≥ 10 years.
- Outcomes:
  - Intraoperative outcomes: splenic injury, splenectomy, gastroesophageal injury, perforation, liver injury, bleeding, infection, pneumothorax, other respiratory-related complications, conversion to open surgery, and death due to surgery.
  - Postoperative outcomes (short- and long-term follow-up): odynophagia, dysphagia, stenosis, gas bloating, vomiting, regurgitation, inability to vomit/belch, heartburn, epigastric/sternal pain, esophageal spasm, reoperation, reasons for reoperation, use of proton pump inhibitors (PPIs), percentage of overall time with pH <4 on 24-hour monitoring, DeMeester score, LES pressure, endoscopy (for monitoring esophageal mucosal

injury), Gastroesophageal Reflux Symptom Scale (GERSS), health-related quality of life (HRQOL), and the General Health Short Form 36 (GH-SF 36).
- Context: clinical and community settings, regardless of geographical location.
- Published full-text article in English.

Search strategy

Searches were conducted in MEDLINE (Ovid), Embase, CINAHL, the Cochrane Library, and Web of Science up until January 20, 2023. The search was performed by medical information experts from the Karolinska Institutet library. No limitations regarding publication dates were implemented. Reference lists of the selected eligible studies were manually searched for other relevant studies. See Appendix A for the detailed search strategy.

Selection of studies

Studies were selected via a thorough process facilitated by the program EndNote™ (Clarivate, Philadelphia, United States of America). First, duplicates were removed by EndNote's built-in function. Second, titles and/or abstracts of the studies were screened by one reviewer (JH). Third, one reviewer (JH) assessed the eligibility of full-text articles using the eligibility criteria listed above. The study was considered the unit of interest and not each published article. Therefore, articles were collated if they originated from the same study.

Data extraction

An electronic data extraction form was developed and used to obtain data. Methods, LNF (intervention), participants, and outcomes in the LNF group were the focus. Data extraction was performed by one reviewer (JH). The template form as well as the data extracted and used are available upon request. If articles repeated results from the same study, they were compared, and data were extracted from only one of them.

Appraisal

Included studies were assessed using the Joanna Briggs Institute (JBI) critical appraisal tool for RCTs [12]. The appraisal was performed independently by two reviewers (JH and SD). Any disagreement was resolved through discussion until consensus was reached.

Data analysis

The objective of this review was to synthesize clinical evidence solely on LNF to understand the clinical safety and performance of this procedure. As previously stated, the comparator arms were not included. Therefore, the scope of this systematic literature re-

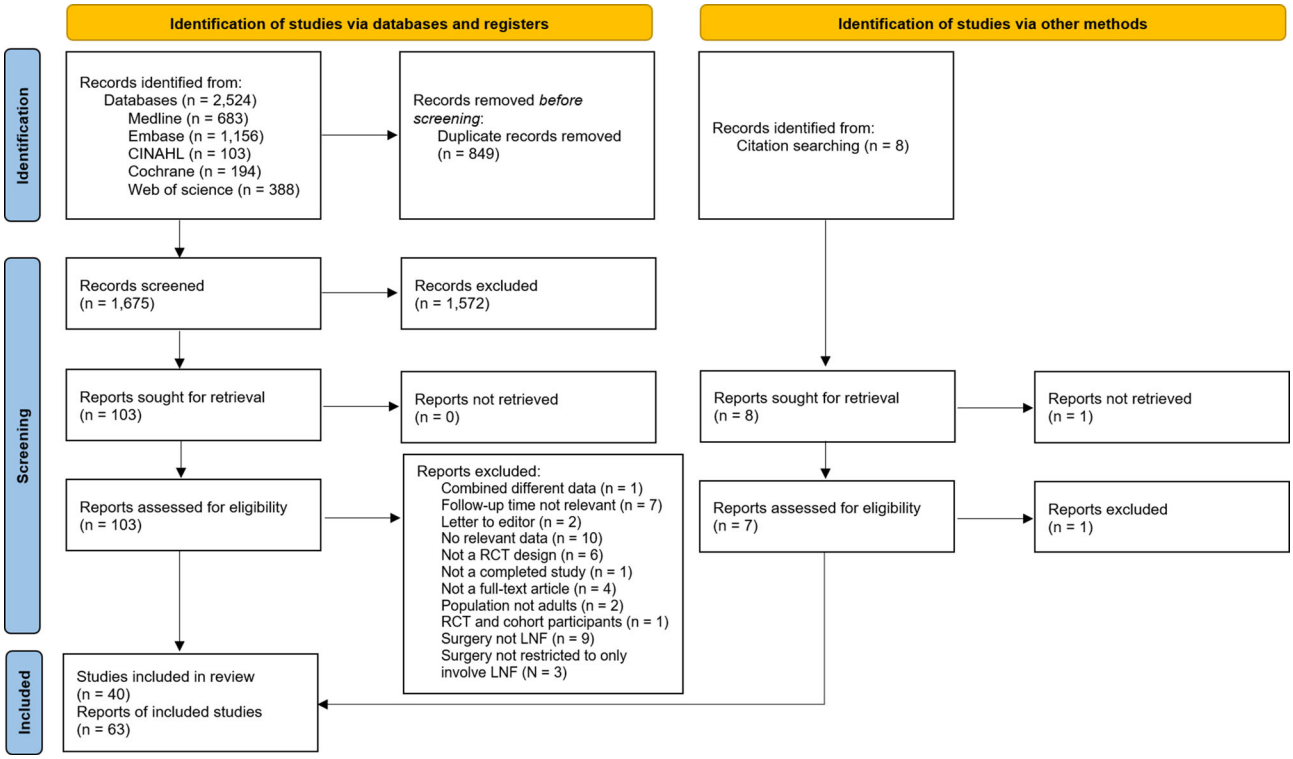

Fig. 1 Search results and workflow of study selection

Table 1 Characteristics of included studies

Study[a]	Country	Baseline		
		Sample size (*n*)	Male (*n*)	Age (years)
Ackroyd et al. (2004) [14]	UK	52	39	Median 42.5
Anvari et al. (2006) [15]	Canada	52	29	Mean 42.9
Attwood et al. (2008) [16] Galmiche et al. (2011) [17] Hatlebakk et al. (2016) [18]	Austria, Belgium, Denmark, France, Germany, Iceland, Italy, Netherlands, Norway, Sweden, UK	288	199	Mean 45
Aye et al. (2012) [19]	USA	46[b]	17	Mean 47.5
Baigrie et al. (2005) [20] Roks et al. (2017) [21]	South Africa	84	49	NR
Blomqvist et al. (2000) [22] Mardani et al. (2009) [23]	Sweden	52	29	Mean 48
Booth et al. (2008) [24]	UK	64	41	Mean 45.3
Cao et al. (2012) [25]	China	50	21	Mean 59.1
Chrysos et al. (2001) [26]	Greece	24	15	Mean 51
Chrysos et al. (2002) [27]	Greece	56	37	Mean 48
Djerf et al. (2016) [28]	Sweden	36	20	Median 47.5
Draaisma et al. (2006a) [29] Broeders et al. (2009) [30] Oor et al. (2017) [31]	Netherlands	98	NR	NR
Draaisma et al. (2006b) [32]	Netherlands	25	17	Median 52.0
Franzén et al. (2005) [33]	Sweden	50	27[c]	Median 48[c]
Granderath et al. (2005) [34]	Austria	50	30	Mean 48.7
Guérin et al. (2007) [35]	Belgium	77	54	NR
Heikkinen et al. (1999) [36]	Finland	22	NR	NR
Håkanson et al. (2019) [37] Analatos et al. (2022) [38]	Sweden	227	134	Mean 50.2
Khan et al. (2009) [39]	UK	61	38	Mean 45
Koch et al. (2012) [40]	Austria	50	30	Mean 49.7
Koch et al. (2013) [41]	Austria	62	35	Mean 50.3
Laine et al. (1997) [42] Salminen et al. (2012) [43]	Finland	55	NR	Mean 47
Laws et al. (1997) [44]	USA	23	10	Mean 45.5
Mahon et al. (2005) [45]	UK	109	71	Median 48
Mickevičius et al. (2008) [46] Mickevičius et al. (2013) [47]	Lithuania	38	17	Mean 49.2
Morino et al. (2006) [48]	Italy	25	18	Mean 46.3
Müller-Stich et al. (2007) [49] Müller-Stich et al. (2009) [50] Lang et al. (2022) [51]	Germany	20	8	Mean 50.5
Nakadi et al. (2006) [52]	Belgium	11	8	Mean 48
Paranyak et al. (2021) [53]	Ukraine	51	26	Mean 50.5
Patterson et al. (2000) [54]	USA	90	53	Mean 47.9
Qin et al. (2013) [55]	China	215	NR	NR
Raue et al. (2011) [56]	Germany	32	NR	NR
Spence et al. (2006) [57] Watson et al. (2012) [58]	Australia	39	19	Mean 45.7
Strate et al. (2008) [59]	Germany	100	NR	NR
Wang et al. (2015) [60]	China	43	20	Mean 57.0
Watson et al. (1997) [61] O'Boyle et al. (2002) [62] Yang et al. (2008) [63] Kinsey-Trotman et al. (2018) [64]	Australia	52	31	Mean 45.3

Table 1 (Continued)

Study[a]	Country	Baseline		
		Sample size (*n*)	Male (*n*)	Age (years)
Watson et al. (1999) [65] Ludemann et al. (2005) [66] Cai et al. (2008) [67] Rudolph-Stringer et al. (2020) [68]	Australia	53	NR	NR
Watson et al. (2001) [69] Wijnhoven et al. (2008) [70] Chew et al. (2011) [71]	Australia	55	NR	NR
Watson et al. (2004) [72] Nijjar et al. (2010) [73]	Australia, New Zealand	52	33	Mean 49
Wenner et al. (2001) [74] Nilsson et al. (2002) [75] Nilsson et al. (2004) [76]	Sweden	30	17	Median 50

NR not reported
[a]Each row corresponds to the same study and population, published in one or more articles
[b]Postoperative sample size
[c]Data presented for per-protocol sample ($n = 45$)

view excluded any comparative analyses such as meta-analysis. Descriptive statistics were used to present the intraoperative, clinical, and objective postoperative results for patients treated with LNF. Dichotomous data were collated for intraoperative and postoperative clinical outcomes. If needed, the data were recalculated as the number of events or percentages. Summary results included only studies with reported outcome data and corresponding sample size. A subanalysis was performed on a subset of studies comparing 10- and 17-year follow-up, where patients acted as their own control. Postoperative PPI use and reoperation were combined to represent treatment failure. Continuous data were collated for objective postoperative outcomes and calculated as weighted averages. The weights were calculated according to each individual study's sample size. Regarding the percentage of overall time with pH < 4, a normal value was defined as < 4.5% [13]. A DeMeester score of < 14.72 was defined as the normal value [13]. Stenosis and esophageal spasm were not reported in the included studies and several postoperative outcomes (i.e., LES pressure, endoscopy, GERSS, HRQOL, and GH-SF 36) were inconsistently reported for the selected follow-ups. These outcomes were subsequently not analyzed nor further reported in this systematic literature review. See Table B.1 for further details.

Results

Results of the search

A total of 2524 records were identified through searching databases, of which 1675 were screened after removal of duplicates. During screening, 1572 records were excluded, and 103 full-text articles were assessed for eligibility. Eight additional records were identified through citation searching, of which seven were assessed for eligibility. In total, 63 articles (with data from 40 RCTs) met the inclusion criteria and were included [14–76]. The flow diagram (Fig. 1) shows the work process for study selection and reasons for exclusion of full-text articles.

Included studies

Characteristics of included studies are summarized in Table 1. This systematic literature review included a total of 2619 participants treated with LNF. When presented, the study population was comprised of between 37% and 75% men, with a mean age of 42.9 to 59.1 years (median 42.5 to 52.0 years). The studies were conducted on five continents, mostly in Europe, and published between 1997 and 2022. Without further description, the comparator was one of the following: open Nissen fundoplication [14, 27, 29, 33, 36, 42, 74], laparoscopic Hill repair [19], laparoscopic anterior 90° fundoplication [57, 72], laparoscopic 120° anterior fundoplication [28], laparoscopic 180° anterior fundoplication [20, 25, 56, 65], laparoscopic 200 to 270° (Toupet) fundoplication [24, 35, 37, 40, 41, 44, 46, 55, 59, 60], robot-assisted LNF [32, 48, 49, 52], laparoscopic Lind fundoplication [39], a variation of LNF [22, 26, 34, 53, 54, 61, 69], or PPI therapy [15, 16, 45]. For the included studies with a variation of LNF, only one was considered as the intervention group and included in this review. The variations considered to be the comparator group and not presented in this review included LNF without division of short gastric vessels [22, 26, 61], LNF with crural closure using simple sutures and mesh hiatoplasty [34], additional prosthetic hiatal closure with a bougie [54], additional anterior hiatal closure [69], and LNF with suturing of the wrap to both diaphragmatic crura or to the body of the stomach [53]. In one study, the intervention group was divided into LNF with a 1.5- or 3-cm wrap, but only data for participants receiving a 3-cm wrap were included [46, 47].

Table 2 Number of intraoperative events

Study	Baseline sample size	Splenic injury/ splenectomy	Gastroesophageal injury/perforation	Liver injury	Bleeding	Respiratory infection	Respiratory complications[a]	Conversion to open surgery	Death
Ackroyd et al. (2004) [14]	52	NR	NR	NR	1	NR	NR	5	0
Anvari et al. (2006) [15]	52	0	0	0	0	NR	NR	0	0
Attwood et al. (2008) [16]	288	NR	NR	NR	NR	NR	17	0	0
Aye et al. (2012) [19]	46	NR	1	NR	NR	NR	NR	NR	0
Baigrie et al. (2005) [20]	84	NR	NR	NR	NR	NR	NR	0	NR
Blomqvist et al. (2000 [22]	52	NR	NR	NR	NR	NR	1	2	NR
Booth et al. (2008) [24]	64	NR	NR	NR	NR	NR	NR	0	0
Cao et al. (2012) [25]	50	0	1	0	0	NR	NR	NR	0
Chrysos et al. (2001) [26]	24	0	0	0	2	NR	NR	0	0
Chrysos et al. (2002) [27]	56	0	0	0	9	NR	NR	0	0
Djerf et al. (2016) [28]	36	NR	NR	NR	NR	NR	NR	1	NR
Draaisma et al. (2006a) [29]	98	NR	NR	NR	NR	NR	NR	6	NR
Draaisma et al. (2006b) [32]	25	2	NR	4	NR	NR	1	2	NR
Franzén et al. (2005) [33]	50	NR	NR	NR	NR	NR	NR	1	0
Granderath et al. (2005) [34]	50	0	0	0	0	NR	NR	0	NR
Guérin et al. (2007) [35]	77	NR	NR	NR	NR	NR	NR	1	0
Heikkinen et al. (1999) [36]	22	NR	NR	NR	2	NR	NR	1	NR
Håkanson et al. (2019) [37]	227	NR	NR	NR	NR	NR	NR	2	0
Khan et al. (2009) [39]	61	NR	NR	NR	NR	NR	NR	0	0
Koch et al. (2012) [40]	50	0	0	0	0	NR	NR	0	NR
Koch et al. (2013) [41]	62	0	0	0	0	NR	NR	0	NR
Laine et al. (1997) [42]	55	NR	2	NR	1	0	NR	5	NR
Laws et al. (1997) [44]	23	NR	NR	NR	NR	NR	NR	0	0
Mahon et al. (2005) [45]	109	2	1	1	NR	NR	NR	1	0
Mickevičius et al. (2008) [46]	38	NR	NR	NR	NR	NR	NR	NR	0
Morino et al. (2006) [48]	25	0	0	0	0	NR	NR	0	0
Müller-Stich et al. (2007) [49]	20	0	0	0	2	NR	NR	0	NR
Nakadi et al. (2006) [52]	11	NR	NR	NR	NR	NR	NR	0	NR
Paranyak et al. (2021) [53]	51	NR	NR	NR	NR	NR	1	0	0
Patterson et al. (2000) [54]	90	2	1	5	1	NR	1	0	0

Table 2 (Continued)

Study	Baseline sample size	Splenic injury/ splenectomy	Gastroesophageal injury/perforation	Liver injury	Bleeding	Respiratory infection	Respiratory complications[a]	Conversion to open surgery	Death
Qin et al. (2013) [55]	215	NR	NR	NR	NR	NR	NR	0	0
Raue et al. (2011) [56]	32	0	0	0	0	NR	NR	0	NR
Spence et al. (2006) [57]	39	NR	NR	NR	NR	NR	3	0	NR
Strate et al. (2008) [59]	100	NR	NR	NR	NR	NR	NR	0	0
Wang et al. (2015) [60]	43	0	0	0	0	NR	NR	0	0
Watson et al. (1997) [61]	52	NR	1	NR	3	NR	NR	4	NR
Watson et al. (1999) [65]	53	NR	NR	NR	NR	NR	NR	1	NR
Watson et al. (2001) [69]	55	NR	NR	NR	NR	NR	NR	0	NR
Watson et al. (2004) [72]	52	1	NR	NR	1	NR	2	2	NR
Wenner et al. (2001) [74]	30	0	1	1	2	0	2	5	NR
Total (n)	*2619*	*7*	*8*	*11*	*24*	*0*	*28*	*39*	*0*
Total percentage[b]	–	*0.9%*	*0.9%*	*1.5%*	*2.9%*	*0.0%*	*4.5%*	*1.6%*	*0.0%*

NR not reported
[a]Includes atelectasis, pneumothorax, CO_2 retention, minor respiratory complication, left subphrenic collection, respiratory failure, emphysema
[b]Only studies with reported data

Intraoperative outcomes

All included studies presented results for at least one intraoperative outcome (Table 2). In total, 78 injuries and other complications occurred. Most were respiration-related complications (4.5%), followed by bleeding (2.9%). Furthermore, 39 cases (1.6%) required conversion to open surgery, reported by 37 articles. Gastroesophageal injury or perforation occurred in 0.9% of the subjects, reported by 17 articles. However, no deaths occurred during LNF surgery. As shown in Table 2, several outcomes were sporadically reported by the included studies, except for conversion to open surgery.

Postoperative outcomes

Heartburn and epigastric/sternal pain were combined into one outcome measure for the purposes of this review, which is referred to as "heartburn or epigastric/sternal pain" from this point on. Appendix B presents some results in more detail.

Results from the two earliest postoperative timepoints were collated into one period, i.e., 4 to 6 weeks after surgery. A summary of postoperative results is shown in Table 3 and presented more elaborately in Supplementary Table B.2. In total, 15 studies reported some result among 656 participants [14, 28, 34, 39, 48, 49, 52–54, 57, 60, 61, 69, 72, 75]. Postoperative events were common, particularly dysphagia (46.1%), gas bloating (32.5%), and heartburn or epigastric/sternal pain (31.9%).

At 6 months, some postoperative events decreased in frequency while others increased among the 584 available participants from 13 of the included studies [14, 22, 24, 32, 33, 39, 46, 53, 61, 65, 69, 72, 74]. These are shown in Table 3 and Supplementary Table B.3. The most common included gas bloating (32.2%), dysphagia (27.9%), and heartburn or epigastric/sternal pain (27.9%).

One year after surgery, 16 studies presented postoperative results among 656 participants [14, 20, 22, 24, 26–28, 34, 35, 39, 42, 47, 50, 52, 57, 73]. The results are shown in Table 3 and Supplementary Table B.4. In general, the overall percentage for each outcome had decreased in comparison to previous measurements. However, some outcomes were still relatively common, such as gas bloating (30.1%), dysphagia (22.4%), inability to vomit/belch (16.4%), and heartburn or epigastric/sternal pain (15.1%).

Results 5 years after operation were reported in nine studies among 504 participants [17, 25, 47, 58, 62, 66, 70, 73, 76]. The data exhibited an increase in the overall percentage for most outcomes, as shown in Table 3 and Supplementary Table B.5. Most participants complained about gas bloating (52.7%), inability to vomit/belch (39.8%), dysphagia (28.9%), and heartburn or epigastric/sternal pain (27.0%).

In six studies, 288 participants were successfully followed for 10 years after surgery and had postop-

erative results [23, 28, 30, 63, 67, 71]. Overall, most of the outcomes continued to increase in frequency at the 10-year follow-up (Table 3 and Supplementary Table B.6). Again, complication rates were substantial for inability to vomit/belch (48.8%), dysphagia (45.3%), gas bloating (44.4%), and heartburn or epigastric/sternal pain (30.9%; Table 3 and Supplementary Table B.6).

More than 10 years after the operation (range 12–20 years), only five studies reported results for a total of 238 participants [21, 31, 43, 64, 68]. The results are presented in Supplementary Table B.6. At this follow-up timepoint, there were substantial rates of dysphagia (55.7%), heartburn or epigastric/sternal pain (53.5%), and gas bloating (49.6%).

A summary of dysphagia and heartburn or epigastric/sternal pain at 10- and 17-year follow-ups with patients acting as their own control is presented in Table 4. These long-term postoperative clinical results were reported in three studies [30, 31, 63, 64, 67, 68]. Almost half of the participants complained about dysphagia 10 years after operation (50.3%) and around a third about heartburn or epigastric/sternal pain (31.6%). At 17 years after surgery with the same patient groups, substantially more participants suffered from dysphagia (65.1%) and heartburn or epigastric/sternal pain (53.5%).

Reoperation after LNF was reported in 21 of the 40 included studies [15, 19, 20, 22, 25, 28–30, 32, 37, 39, 41, 42, 45–47, 49, 50, 57, 58, 61–63, 65–67, 69–74, 76]. During both short- and long-term follow-up, reoperations were prevalent but to different extents (Table 5 and Supplementary Table B.7). The overall percentage of reoperations was 2.3% up to 4 to 6 weeks postoperatively, which increased to 6.7% up to 1 year postoperatively and to 16.3% up to 10 years postoperatively. The number of studies reporting reoperation differed for each follow-up, mostly presenting 1-year results. Reoperations were mainly for two reasons: (prolonged) dysphagia and recurrent reflux symptoms. Several studies also reported reoperations due to hiatal hernia (including herniation of the wrap, incisional hernia, paraesophageal hiatal hernia, and recurrence of hiatal hernia).

Postoperative PPI medication use was presented in 18 studies, as shown in Table 5 and Supplementary Table B.8 [15, 17, 19, 21, 23, 25, 28–30, 37, 38, 42, 46, 47, 50, 51, 58, 62, 63, 66, 67, 70, 71, 73, 76]. PPI use was only reported in this review for follow-up periods ≥ 1 year. At 1 and 5 years after operation, there were similar rates for PPI use (12.3% and 11.9%, respectively), which increased to 23.3% at 10-year follow-up and to 23.5% at 12 to 15 years postoperatively.

When looking at the total failure rate, the most indicative figure is given by combining patient reoperations with PPI use (Table 5). Reoperations plus PPI use presented in 19.0% at 1 year postoperatively, with a similar rate after 5 years of 20.6%. However, 39.6% required PPIs and/or a reoperation after 10 years.

The percentage of total time with pH < 4 on 24-hour monitoring and DeMeester score were presented in seven studies for the 6-month and 1-year follow-ups [15, 22, 25, 33, 34, 42, 46]. However, the results were merged, as shown in Table 6. Regarding the percentage of total time with pH < 4, the weighted average of means was 3.3%, and the weighted average of means for the DeMeester score was 12.6. These average numbers are normal but represent high values for an average value of acid exposure. The number of failures was generally not disclosed.

Appraisal

The critical assessment is summarized in Supplementary Table B.9 and the query domains were mostly fulfilled in the included studies. However, multiple articles did not provide enough information, resulting in an unclear assessment for several domains. Out of the 40 studies included in this review, 10 studies did not fulfill three or more query domains [14–19, 22, 33, 41, 45, 51, 53].

Discussion

The purpose of this systematic literature review was to investigate the postoperative safety and performance of LNF in adult patients with GERD, since exhaustive scrutiny is lacking in the current evidence base. Out of the 1675 articles included following elimination of duplicates, 63 articles were selected, covering 40 different RCTs of LNF at various timepoints. These studies provided information on intraoperative and/or postoperative outcomes ranging from 4 weeks to more than 17 years postoperatively. Altogether, the studies included 2619 participants.

The overall number of anti-reflux surgeries (i.e., LNF) performed worldwide has decreased over recent decades, and LNF procedures are performed in limited numbers relative to the large acid reflux treatment field [3]. This is most likely due to the imbalance between symptom control and the occurrence of complications that has limited the number of patients referred for surgery by medical doctors and general practitioners [3]. One reason for the reduction in the number of Nissen procedures may be that approximately 40–50% of LNF patients suffered from an inability to belch or vomit and had gas bloating after 5 years, as noted in the Results section of the present review.

The results indicate that rather few complications and injuries occurred during surgery, estimated at 5.5% ($n = 78$), and no deaths occurred. A systematic review by Salman et al. indicated a slightly higher rate of perioperative events (7.5%) during LNF, but with similar types of complications except conversion to open surgery, which was omitted [6]. Another review by Broeders et al. reported no deaths associated with LNF surgery [10]. In our review, all but three included

Table 3 Summary of clinical postoperative events at 4 to 6 weeks, 6 months, 1 year, 5 years, and 10 years follow-up[a]

Postoperative outcome	4–6 weeks[b]	6 months[b]	1 year[b]	5 years[b]	10 years[b]
Odynophagia	18.7%	8.0%	13.8%	16.0%	–[c]
Dysphagia	46.1%	27.9%	22.4%	28.9%	45.3%
Gas bloating	32.5%	32.2%	30.1%	52.7%	44.4%
Vomiting	7.9%	3.3%	2.6%	0.0%	7.0%
Regurgitation	14.6%	7.6%	8.4%	5.4%	18.3%
Inability to vomit/belch	31.3%	27.1%	16.4%	39.8%	48.8%
Heartburn or epigastric/sternal pain	31.9%	27.9%	15.1%	27.0%	30.9%
Number of studies	*15*	*13*	*16*	*9*	*6*

[a]See detailed tables per follow-up point in Appendix B
[b]Total number of studies at each follow-up timepoint; 4–6 weeks: 15 studies; 6 months: 13 studies; 1 year: 16 studies; 5 years: 9 studies; 10 years: 6 studies. The number of studies for each outcome varies because certain symptoms were not reported in some studies
[c]Not enough data to safely judge the symptom odynophagia after 10 years

studies reported on the frequency of conversion to open surgery, which was required in 1.6% of the cases ($n=39$). However, most of these conversions (64%) were reported in five studies [14, 29, 42, 61, 74]. These conversions were performed between 1992 and 2000, i.e., somewhat earlier than in the remainder of the studies. Overall, these operations were performed about a decade ago. Therefore, the presented intraoperative events may correlate with surgical skill.

The data show that the complication rates exhibit a U-shaped curve in general, with the best results occurring at 1 year after surgery. Such complications include dysphagia, vomiting, the inability to vomit/belch, and heartburn or epigastric/sternal pain (Table 3 and Fig. B.1a–d in Appendix B). Symptoms were present 4 to 6 weeks after surgery, with a decreasing trend after 6 months to the lowest amount at 1 year, followed by an increase again at 5 years that continued to 10 years or more postoperatively.

The U-shaped curve of complication rates can be exemplified further by the two symptoms dysphagia and heartburn or epigastric/sternal pain.

Dysphagia is a well-known side effect related to compression of the food passageway that occurs with the Nissen wrap. At 4 to 6 weeks after surgery, 46.1% of participants presented with dysphagia, which reduced to 27.9% at 6 months and further decreased to 22.4% at 1 year. However, the dysphagia rate increased again to 28.9% after 5 years and even further to 45.3% after 10 years (Table 3 and Supplementary Table B.6). Additionally, the sub-analysis on patients acting as their own control showed a notable increase in the percentage of dysphagia, from 50.3% at 10 years to 65.1% at 17 years. Like the present results, Salman et al. displayed that 16.2% of participants had dysphagia 1 year after LNF surgery [6]. However, only 9.8% of the patients in that review had dysphagia >12 months afterwards, a rate which is substantially lower than the results in our review (e.g., 22.4% at 1-year follow-up). However, Broeders et al. reported that 13.5% of LNF patients had dysphagia ≥1 year after their surgery [9]. On the other hand, Du et al. showed that 40% of patients had dysphagia more than 5 years after LNF surgery [8], which is higher than in our results (28.9%). However, another review reported a dysphagia rate of 33% at 5-year follow-up [10], in line with our results.

Heartburn or epigastric/sternal pain displayed a similar U-shaped curve, whereby 31.9% of the participants presented with symptoms 4 to 6 weeks after surgery. At 6 months, 27.9% experienced these symptoms, a figure which decreased to 15.1% at 1-year follow-up. However, this symptomology increased to 27.0% at 5 years and further to 30.9% at 10 years (Table 3 and Supplementary Table B.6). Furthermore, the summary of results at 10- and 17-year follow-ups with patients acting as their own control showed a notable increase in the rate of heartburn or epigastric/sternal pain to 31.6% at 10 years that progressed to 53.5% at 17 years. Broeders et al. reported that 6.3% of patients experienced heartburn at the 1-year follow-up [10]. Our results are substantially higher (15.1%). In the same review by Broeders et al., the authors reported that 11.8% of patients had heartburn at the 5-year follow-up [10]. Furthermore, Du et al. showed that 13.1% of patients had heartburn more than 5 years after LNF surgery [8]. These are considerably lower rates than we found (27.0% at 5 years and 30.9% at 10 years; Table 3 and Supplementary Table B.6). However, these previous reviews only included three studies for this endpoint, which might explain the differences in results. These outcomes are also related to how many of the failure patients were reoperated.

Gas bloating and regurgitation did not display a pattern that was appreciated as clearly, though the highest numbers of events occurred after 5 years and 10 years (52.7% and 18.3%, respectively). Previous research indicated that more than one third of LNF patients had gas bloating postoperatively [6], and another review reported 18% at the 1-year follow-up [10]. Broeders et al. reported that 35.9% had gas bloating among LNF patients with at least 1 year of follow-up [9]. These results are in line with the present review's results 1 year after LNF surgery (30.1%). Furthermore, a previous review reported that 48% experienced gas bloating after 5 years [10], which is similar to our

Table 4 Summary of clinical postoperative events at 10-year and 17-year follow-ups with patients acting as their own control

Study[a]	Baseline sample size, *n*	Follow-up sample size, *n*	Follow-up time-point	Dysphagia, *n* / %	Heartburn or epigastric/sternal pain, *n* / %
10-year results					
Broeders et al. (2009) [30]	98	79	10 years	42	32
Cai et al. (2008) [67]	53	48		25	7
Yang et al. (2008) [63]	52	44		19	15
Total, n / %	*203*	*171*		*50.3%*	*31.6%*
17-year results, the same study samples as 10-year results					
Oor et al. (2017) [31]	98	58	17 years	28	25
Rudolph-Stringer et al. (2020)[b] [68]	53	41		29	17
Kinsey-Trotman et al. (2018) [64]	52	30		25	26
Total, n / %	*203*	*129*		*65.1%*	*53.5%*

[a]Same study population in Broeders et al. (2009) and Oor et al. (2017), in Cai et al. (2008) and Rudolph-Stringer et al. (2020), and in Yang et al. (2008) and Kinsey-Trotman et al. (2018). Therefore, the table displays the same patient group at the follow-up timepoints
[b]Sample size, dysphagia $n = 38$, heartburn or epigastric/sternal pain $n = 39$

Table 5 Summary of reoperation and PPI medication use at 4 to 6 weeks, 6 months, 1 year, 5 years, 10 years, and 12 to 15 years after operation

	4 to 6 weeks (%)	6 months (%)	1 year (%)	5 years (%)	10 years (%)	12 to 15 years (%)
Reoperation	2.3	6.3	6.7	8.7	16.3	*N/A*
PPI medication	*N/A*	*N/A*	12.3	11.9	23.3	23.5
Total failure	*N/A*	*N/A*	*19.0*	*20.6*	*39.6*	*N/A*

PPI proton pump inhibitor, *N/A* not applicable, i.e. no data were reported for the selected outcome

Table 6 pH results at the 6-month and 1-year follow-ups

Study	Follow-up	Sample size, *n*	Results
Mean percentage total time pH <4 in 24-h monitoring			
Anvari et al. (2006) [15]	1 year	44	2.5%
Blomqvist et al. (2000) [22]	6 months	48	1.9%
Franzén et al. (2005) [33]	6 months	42	6.1%
Laine et al. (1997) [42]	1 year	18	2.5%
Total	–	*152*	*3.3% (weighted average of means)*
Mean DeMeester score			
Cao et al. (2012) [25]	6 months/1 year	50	18.7[a]
Granderath et al. (2005) [34]	1 year	50	9.1
Mickevičius et al. (2008) [46]	1 year	14	2.9
Total	–	*114*	*12.6 (weighted average of means)*

[a]Average of 6-month and 1-year mean DeMeester score

5-year data (52.7%). In this review from the year 2013 by Broeders et al., 4.9% of patients reported regurgitation at the 1-year follow-up [10], which is lower than our result (8.4%). We reported data from eight studies, whereas the previous review only provided data from three studies, which may explain the differing results.

Reoperations occurred throughout the entire study period and continued to increase with longer follow-up times, while PPI use was similar at 1 and 5 years after surgery, followed by a distinct increase after 10 years (Table 5 and Supplementary Tables B.6 and B.7). Whether PPI use is a suitable outcome for assessment may be scrutinized; however, it serves as an indication of the treatment effect [77]. Of note, around one fifth of the patients (19.0%) required reoperation and/or PPI use 1 year postoperatively, and more than one third (39.6%) required PPIs and/or reoperation after 10 years. Most studies reported that the reason for reoperation was due to dysphagia or recurrent reflux symptoms. This was expected based on the prevalent postoperative data and the U-shaped curves displayed in this review. Evidence from a previous review indicated a similar rate of PPI use postoperatively (13.1%) [6]. Another review reported PPI use in 7.4% of LNF patients at the 1-year follow-up and in 10% at the 5-year follow-up [10]. On the contrary, we found higher rates of PPI use (12.3% and 11.9%, respectively). However, firstly, we based our results on eight studies compared to the two to three in the review by Broeders et al. [10].

Secondly, one needs to keep in mind that the number of PPI users depends on how many patients have been reoperated. The higher the reoperation rate, the lower the number of PPI users. This is why the combination of these two data points, as reported, is valuable. Postoperatively, Salman et al. showed that 4.5% needed reoperation, which is a lower rate than most postoperative rates presented in this review [6]. However, Salman et al. combined studies with follow-up periods ranging from 3 months to 15 years, which might explain the difference in rates. Another review by Broeders et al. from 2010 indicated that 7.0% of patients required reoperation after at least 1 year following LNF [9], which is similar to our results after 1 year (6.7%). Most other reviews included only a few studies, meanwhile, we included 17 studies. Furthermore, our inclusion of randomized studies provided more robust data that found lower reoperation rates if failure patients were kept on PPIs.

Despite pH monitoring being considered the gold standard modality for diagnosis of GERD [13], the frequency of 24-hour pH monitoring test failure was generally not reported in the included studies. Instead, only the weighted average results were presented, demonstrating normal values for acid exposure 6 to 12 months after surgery [13]. These average numbers were normal but occupy the higher end of normal limits in terms of acid exposure. However, due to the invasive nature of most objective measurements, it was expected that only a couple of these outcomes were possible for inclusion in evidence synthesis. Like the results presented in this review, previous research indicates a normal percentage of time with pH <4 and normal DeMeester scores following LNF on average, albeit with results in the upper end of the normal result range [4, 6, 10].

The results of this review indicate that side effects and complications were present during both short- and long-term follow-up after LNF. In general, the clinical postoperative results suggested that following surgery, it took about 1 year before patients achieved maximally optimal results. Nevertheless, worsening of the rates of symptoms and complications continued for more than 10 years afterwards.

Appraisal indicated that most of the studies fulfilled the domains stated in the JBI critical appraisal tool [12]. However, critical information was missing from multiple articles, causing speculation of the evidence to some extent. The omission of information cannot be fully explained by the journals' restrictions; for instance, word limit restrictions are one such consideration.

Strengths and limitations

To only include RCTs is a strength of this study, since the review was spared from inherent methodological issues associated with observational studies. Numerous subjective and objective outcomes were studied, enabling a more thorough perspective of the procedure. This was further enhanced by including both short- and long-term specific follow-up timepoints. The appraisal was performed by two independent reviewers, thus ensuring a rigorous assessment of the studies included. Descriptive statistics were utilized for all statistical analyses, since to test hypotheses in our setting would extensively use the same data on a repeated basis, resulting in redundant hypothesis testing. We could have used, e.g., Bonferroni corrections to resolve that, but adding complexity to the analysis where there are missing data (e.g., Table B.3) could make the analysis opaque from a statistical point of view. The only feasible solution would be to make the claim that the missing data are missing at random, and even if that does apply to some studies, it certainly does not for all. As a result, we chose not to perform a more in-depth statistical analysis in this review.

We also acknowledge some limitations. Mainly, our choice to focus solely on LNF and not include the comparator arm(s) is a limitation, as an analysis of comparative evidence between LNF and other treatment options was not conducted, although this may provide objective information to help in clinical decision-making. We failed to synthesize several outcomes (Table B.1), which highlights the lack of evidence in published studies pertaining to LNF. There were slight variations of the LNF technique that may potentially affect generalizability. However, the included trials described the surgical procedures to various degrees, with different levels of detail, making categorization insufficient. Further, we were limited by the inconsistency in endpoint reporting. For instance, 16 studies provided data at the 1-year follow-up, but only four trials presented odynophagia results (Table B.4). Additionally, 24-hour pH monitoring results were combined for the 6- and 12-month follow-ups, which slightly reduced resolution and context. However, this outcome was surprisingly infrequent and was therefore deemed the best option. Some portions of the systematic literature review were conducted by one reviewer, although double-checked, which may affect the syntheses and robustness.

Conclusion

Although LNF is considered the gold standard in anti-reflux surgery and has been a recurrent research topic for many decades, a complete review of the literature has not been comprehensively performed. The safety profile presented in this systematic literature review demonstrates a limited number of serious surgical complications and a reasonable number of reoperations. The performance of LNF varies over time, with an increasing number of patients taking PPIs and most symptoms presenting as a U-shaped curve with the lowest rates at 1 year. Complication rates were substantially higher at 5 years, whereby

participants from nine randomized trials presented with gas bloating (52.7%), inability to vomit/belch (39.8%), dysphagia (28.9%), and heartburn or epigastric/sternal pain (27.0%). The available postoperative data up to 17 years indicate that the performance of Nissen fundoplication dissipates in the long term. Several reported events could, at least partly, be attributed to the compression of the food passageway that is associated with the fundal wrap technique of Nissen fundoplication.

The complications and adverse events indicate an unmet need, where newer treatment options may contribute to reducing the treatment gaps. Surgeons and patients should take this review into consideration when selecting treatment for gastroesophageal reflux disease.

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Conflict of interest The work was conducted from 2017 to 2023, of which the main work was conducted during the years 2017–2018. During this period, the primary researcher (J. Hoffsten) was not an employee of the funding company but employed at the Karolinska Institutet. The authors J. Hoffsten (since 2020) and S. Das (since 2023) are consultants at the funding company and affiliated with the Karolinska Institutet. J. Zehetner, S.F. Schoppmann, and J.C. Lipham declare that they have no competing interests.

Appendix A

Search strategy

Table A.1 Search strategy in MEDLINE (Ovid), Embase, CINAHL, Cochrane library, and Web of Science

MEDLINE (Ovid)	
Date of search: 2017-09-08 Number of hits: 522 Date of search: 2019-09-13 Number of hits: 566. Limit 40 to yr="2017-Current": 66 Date of search: 2020-04-14 Number of hits: 589. Limit 40 to dt="20190912-20200414": 15 Date of search: 2021-06-11* Number of hits: 617. Limit 40 to dt="20200403-20210611": 18 *- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to June 10, 2021 Date of search: 2023-01-20* Number of hits: 665. Limit 40 to ed="20210611-20230120": 62 *- Database(s): Ovid MEDLINE(R) ALL 1946 to January 19, 2023	Field tags: .fs. = Floating sub-heading .pt. = Publication type .ti,ab, kf. = Title, abstract & keyword heading word / = MeSH, not exploded exp / = MeSH, exploded
1. exp Gastroesophageal Reflux/ 2. (GER* or GOR* or Barrett*).ti,ab,kf. 3. ((gastro* or oesophag* or esophag* or disease*) adj2 reflux*).ti,ab,kf. 4. 1 or 2 or 3 5. exp Laparoscopy/ 6. (laparoscop* or abdominoscop* or celioscop* or peritoneoscop*).ti,ab,kf. 7. 5 or 6 8. exp Fundoplication/ 9. (fundoplicat* or nissen* or rosetti* or rossetti* or dor* or toupet*).ti,ab,kf. 10. (fund* adj2 wrap*).ti,ab,kf. 11. 8 or 9 or 10 12. 4 and 7 and 11 13. (ae or to or po or co).fs. 14. (safe or safety).ti,ab. 15. side effect$.ti,ab. 16. ((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. 17. exp product surveillance, postmarketing/ 18. exp adverse drug reaction reporting systems/ 19. exp clinical trials, phase iv/ 20. exp poisoning/ 21. exp substance-related disorders/ 22. exp drug toxicity/ 23. exp abnormalities, drug induced/ 24. exp drug monitoring/ 25. exp drug hypersensitivity/ 26. (toxicity or complication$ or noxious or tolerability).ti,ab. 27. exp Postoperative Complications/ 28. exp Intraoperative Complications/ 29. or/13-28 30. 12 and 29 31. randomized controlled trial.pt. 32. controlled clinical trial.pt. 33. randomized.ab. 34. placebo.ab. 35. drug therapy.fs. 36. randomly.ab. 37. trial.ab. 38. groups.ab. 39. or/31-38 40. 39 and 30	
Embase	
Date of search: 2017-09-07 Number of hits: 739 Date of search: 2019-09-13 Number of hits: 804. [2017-2019]/py: 165 Date of search: 2020-04-14 Number of hits: 837. #39 AND [13-9-2019]/sd NOT [15-4-2020]/sd: 42 Date of search: 2021-06-11 Number of hits: 907. #39 AND [3-4-2020]/sd NOT [11-6-2021]/sd: 87 Date of search: 2023-01-20 Number of hits: 1,016. #39 AND [11-6-2021]/sd NOT [20-1-2023]/sd: 123	Field tags: :ti,ab = Title & abstract /exp = Emtree term, exploded /de = Exact Emtree heading

Table A.1 (Continued)

#1 'gastroesophageal reflux'/exp #2 (ger* OR gor* OR barrett*):ab,ti #3 ((gastro* OR oesophag* OR esophag* OR disease*) NEAR/2 reflux*):ab,ti #4 #1 or #2 or #3 #5 'laparoscopy'/exp #6 (laparoscop* OR abdominoscop* OR celioscop* OR peritoneoscop*):ab,ti #7 #5 or #6 #8 'fundoplication'/exp #9 (fundoplicat* OR nissen* OR rosetti* OR rossetti* OR dor* OR toupet*):ab,ti #10 (fund* NEAR/2 wrap*):ab,ti #11 #8 or #9 or #10 #12 #4 and #7 and #11 #13 (safe OR safety):ti,ab #14 (side NEXT/1 effect*):ti,ab #15 ((adverse OR undesirable OR harms* OR serious OR toxic) NEAR/3 (effect* OR reaction* OR event* OR outcome*)):ti,ab #16 'postmarketing surveillance'/exp #17 'drug surveillance program'/exp #18 'phase 4 clinical trial (topic)'/exp #19 'intoxication'/exp #20 'addiction'/exp #21 'drug toxicity'/exp #22 'congenital malformation'/exp #23 'drug monitoring'/exp #24 'dress syndrome'/exp #25 'drug hypersensitivity'/exp #26 (toxicity OR complication* OR noxious OR tolerability):ti,ab #27 'postoperative complication'/exp #28 'peroperative complication'/exp #29 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 #30 'control group'/de #31 'controlled study'/exp #32 'double blind procedure'/de #33 'single blind procedure'/de #34 'randomized controlled trial'/exp #35 'triple blind procedure'/de #36 (case* NEAR/2 (control* OR comparison*)):ab,ti #37 ('control group*' OR 'controlled stud*' OR 'double blind' OR 'single blind' OR 'triple blind' OR randomized OR randomised OR randomly OR placebo OR trial*):ab,ti #38 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 #39 #12 AND #29 AND #38
CINAHL (Ebsco)

Date of search: 2017-09-08 Number of hits: 21 Date of search: 2019-09-13 Number of hits: 150. [2017-2019]/py: 36 Date of search: 2020-04-14 Number of hits: 177. Limiters - Published Date: 20190901-: 11 Date of search: 2021-06-11 Number of hits: 191. Limiters - Published Date: 20200401-: 9 Date of search: 2023-01-20 Number of hits: 217. Limited to: EM 20210611- OR ZD "in process": 26	Field tags: AB = Abstract MH = Cinahl subject heading MH+ = Cinahl subject heading, exploded TI = Title

Table A.1 (Continued)

S1. (MH ″Gastroesophageal Reflux″)
S2. TI(GER* OR GOR* or Barrett*) OR AB(GER* OR GOR* OR Barrett*)
S3. ((TI((gastro* OR oesophag* OR esophag* OR disease*) AND reflux*)) OR (AB(gastro* OR oesophag* OR esophag* OR disease*) N2 reflux*))
S4. S1 OR S2 OR S3
S5. (MH ″Laparoscopy″)
S6. TI(laparoscop* or abdominoscop* or celioscop* or peritoneoscop*) OR AB(laparoscop* or abdominoscop* or celioscop* or peritoneoscop*)
S7. S5 or S6
S8. (MH ″Fundoplication″)
S9. TI(fundoplicat* or nissen* or rosetti* or rossetti* or dor* or toupet*) OR AB(fundoplicat* or nissen* or rosetti* or rossetti* or dor* or toupet*)
S10. TI(fund* N2 wrap*) OR AB(fund* N2 wrap*)
S11. S8 OR S9 OR S10
S12. (MH ″Postoperative Complications+″)
S13. (MH ″Intraoperative Complications+″)
S14. TI((adverse or undesirable or harms* or serious) N3 (effect* or reaction* or event* or outcome*)) OR AB(((adverse or undesirable or harms* or serious) N3 (effect* or reaction* or event* or outcome*)))
S15. TI(″side effect*″) OR AB(″side effect*″)
S16. TI(safe or safety) OR AB(safe or safety)
S17. S12 OR S13 OR S14 OR S15 OR S16
S18. ((MH ″Random Assignment″) or (MH ″Random Sample+″) or (MH ″Crossover Design″) or (MH ″Clinical Trials+″) or (MH ″Comparative Studies″) or (MH ″Control (Research)+″) or (MH ″Control Group″) or (MH ″Factorial Design″) or (MH ″Quasi-Experimental Studies+″) or (MH ″Placebos″) or (MH ″Meta Analysis″) or (MH ″Sample Size″) or (MH ″Research, Nursing″) or (MH ″Research Question″) or (MH ″Research Methodology+″) or (MH ″Evaluation Research+″) or (MH ″Concurrent Prospective Studies″) or (MH ″Prospective Studies″) or (MH ″Nursing Practice, Research-Based″) or (MH ″Solomon Four-Group Design″) or (MH ″One-Shot Case Study″) or (MH ″Pretest-Posttest Design+″) or (MH ″Static Group Comparison″) or (MH ″Study Design″) or (MH ″Clinical Research+″)) or (clinical nursing research or random* or cross?over or placebo* or control* or factorial or sham* or meta?analy* or systematic review* or blind* or mask* or trial*)
S19. S4 AND S7 AND S11 AND S17 AND S18

Cochrane Library (Wiley)

Date of search: 2017-09-07 Number of hits: 146; Cochrane Reviews (4), Trials (128), Other Reviews (7), Economic Evaluations (7) Date of search: 2019-09-13 Number of hits: Cochrane Reviews (4), Cochrane Protocols (1), Trials (148). 2017-2019: Cochrane Reviews (0), Cochrane Protocols (0), Trials (26) Date of Search: 2020-04-14 Number of hits: Cochrane Reviews (4), Cochrane Protocols (1), Trials (120). 2019-2020: Cochrane Reviews (0), Cochrane Protocols (0), Trials (3) – though 0 after 20190913 Date of Search: 2021-06-11 Number of hits 192: Cochrane Reviews (8), Cochrane Protocols (1), Trials (183). 2019-2020: Cochrane Reviews (0), Cochrane Protocols (0), Trials (13) Date of Search: 2023-01-20 Number of hits 197: Cochrane Reviews (8), Cochrane Protocols (1), Trials (188). With Cochrane Library publication date from Jun 2021 to Jan 2023 Cochrane Reviews (0), Cochrane Protocols (0), Trials (9)	Field tags: :ti,ab,kw = Title, abstract & keywords

1. (GER* or GOR* or Barrett):ti,ab,kw
2. ((gastro* or oesophag* or esophag* or disease*) NEAR/2 reflux*):ti,ab,kw
3. #1 OR #2
4. (laparoscop* or abdominoscop* or celioscop* or peritoneoscop*):ti,ab,kw
5. (fundoplicat* or nissen* or rosetti* or rossetti* or dor* or toupet*):ti,ab,kw
6. (fund* NEAR/2 wrap*)
7. #5 OR #6
8. #3 AND #4 AND #7
9. (safe or safety):ti,ab
10. (″side effect″ or ″side effects″):ti,ab
11. ((adverse or undesirable or harms* or serious or toxic) NEAR/3 (effect* or reaction* or event* or outcome*)):ti,ab
12. #9 OR #10 OR #11
16. #8 AND #15

Table A.1 (Continued)

Web of Science	
Date of search: 2017-09-08 Number of hits: 277 Date of search: 2019-09-13 Number of hits: 313. Refined by: PUBLICATION YEARS: (2019 OR 2018 OR 2017): 56 Date of search: 2020-04-14 Number of hits: 310. Refined by: PUBLICATION YEARS: (2019 OR 2020): 15 Date of search: 2021-06-11 Number of hits: 320. Refined by: PUBLICATION YEARS: (2020 OR 2021): 17 Date of search: 2023-01-20 Number of hits: 334. Restricted to LD=(2021-06-11/2023-01-20): 23	Field tags: TS = Topic
#1. TS=((GER* or GOR* or Barrett* or ((Gastro* or oesophag* or esophag* or disease*) and reflux*))) #2. TS=((laparoscop* or abdominoscop* or celioscop* or peritoneoscop*)) #3. TS=((fundoplicat* or nissen* or rosetti* or rossetti* or dor* or toupet* or (fund* NEAR/2 wrap*))) #4. TS=((safe* OR ″side effect*″ OR ((adverse or undesirable or harm* or serious) NEAR/3 (effect* or reaction* or event* or outcome*)) OR ((postoperat* OR intraoperat* OR peroperat*) NEAR/3 complication*))) #5. TS=(″clinical trial*″ OR ″research design″ OR ″comparative stud*″ OR ″evaluation stud*″ OR ″controlled trial*″ OR random* OR placebo* OR ″single blind*″ OR ″double blind*″) #6. #1 AND #2 AND #3 AND #4 AND #5	

Appendix B

Supplementary tables and figures

Table B.1 Outcomes excluded from data analysis and reporting

Outcome	4–6-week follow-up	6-month follow-up	1-year follow-up	5-year follow-up	≥ 10-year follow-up
Stenosis	0	0	0	0	0
Esophageal spasm	0	0	0	0	0
LES pressure	0	4[a]	5[c]	3[e]	0
Endoscopy	1	4	5	3	1
GERSS	0	0	2	0	1
HRQOL	0	2[b]	7[d]	3[f]	4[g]
GH-SF 36	1	0	2	1	0

[a]Presented in studies as mean LES pressure (mm Hg; 3 studies) and end-expiratory LES pressure (kPa; 1 study)
[b]Studies used general quality-of-life measurement (visual analog scale [VAS]; 1 study), or the PGWB and GRSR (1 study)
[c]Presented in studies as mean LES pressure (4 studies), results only presented in figures without numbers (1 study)
[d]Studies used QOLRAD (3 studies), PGWB and GSRS (1 study), GIQLI (1 study), and EQ-5D (1 study)
[e]Presented in studies as mean LES pressure (mm Hg; 1 study) and end-expiratory LES pressure (kPa; 1 study)
[f]Studies used general quality of life measurement (VAS; 1 study), QOLRAD (1 study), and PGWB (1 study)
[g]Studies used general quality of life measurement (VAS; 2 studies)and PGWB (2 studies)

Table B.2 Number of clinical postoperative events at the 4–6-week follow-up

Study	Baseline sample size, *n*	Follow-up sample size, *n*	Odynophagia, *n*	Dysphagia, *n*	Gas-bloating, *n*	Vomiting, *n*	Regurgitation, *n*	Inability to vomit/belch, *n*	Heartburn or epigastric/sternal pain, *n*
Ackroyd et al. (2004)	52	51	6	31[a]	9[b]	2	2	6	17
Djerf et al. (2016)	36	36	NR	NR	NR	NR	NR	29	NR
Granderath et al. (2005)	50	50	NR	2	NR	NR	2	NR	1
Khan et al. (2009)	61	56	12	30[c]	14[b]	3	1	0	7
Morino et al. (2006)	25	25	NR	3	NR	NR	NR	NR	NR
Müller-Stich et al. (2007)	20	20	NR	4	NR	NR	NR	NR	NR
Nakadi et al. (2006)	11	11[d]	NR	2[e]	NR	NR	NR	NR	NR
Nilsson et al. (2002)	30	25	NR	10	NR	NR	NR	NR	NR
Paranyak et al. (2021)	51	51	NR	19[f]	NR	NR	NR	NR	NR
Patterson et al. (2000)	90	90[4]	NR	64	NR	NR	NR	NR	NR
Spence et al. (2006)	39	39	13	27[e]	18[b]	7	15	NR	20
Wang et al. (2015)	43	43	NR	12	13	NR	6	9	6
Watson et al. (1997)	52	52[d]	7	29[c]	26[b]	5	14	22	30
Watson et al. (2001)	55	55[d]	8	32[c]	19[b]	7	12	14	18
Watson et al. (2004)	52	52[d]	11	21	14[b]	0	6	28	28
Total (n)	*667*	*656*	*57*	*286*	*113*	*24*	*58*	*108*	*127*
Total percentage[g]	–	–	*18.7%*	*46.1%*	*32.5%*	*7.9%*	*14.6%*	*31.3%*	*31.9%*

NR not reported
[a]Lumpy solids: 25; soft solids: 4; liquids: 2
[b]Epigastric bloat
[c]Lumpy solids
[d]Baseline sample size, no follow-up sample size presented
[e]Solids
[f]Moderate or severe
[g]Only studies with reported data

Table B.3 Number of clinical postoperative events at the 6-month follow-up

Study	Baseline sample size, *n*	Follow-up sample size, *n*	Odynophagia, *n*	Dysphagia, *n*	Gas bloating, *n*	Vomiting, *n*	Regurgitation, *n*	Inability to vomit/belch, *n*	Heartburn or epigastric/sternal pain, *n*
Ackroyd et al. (2004)	52	40	1	10[a]	10[b]	1	0	4	6
Blomqvist et al. (2000)	52	48	NR	10	24	NR	0	NR	0
Both et al. (2008)	64	61	17[c]	21	17	NR	13	8	43
Draaisma et al. (2006b)	25	25	NR	2	NR	NR	NR	NR	NR
Franzén et al. (2005)	50	45	NR	8	NR	NR	NR	12	4
Khan et al. (2009)	61	49	0	14[d]	3[b]	3	3	1	6
Mickevičius et al. (2008[e])	38	30	NR	6	NR	NR	NR	NR	NR
Paranyak et al. (2021)	51	49	NR	11[f]	NR	NR	NR	NR	NR
Watson et al. (1997)	52	52[g]	2	15	21[b]	0	3	28	15
Watson et al. (1999)	53	53	1	24[h]	15[b]	1	1	19	22
Watson et al. (2001)	55	55[g]	3	19[d]	18[b]	3	6	14	16
Watson et al. (2004)	52	52[g]	5	11	24[b]	2	6	22	21
Wenner et al. (2001)	30	25	NR	12	NR	NR	1	9[i]	1
Total (n)	*635*	*584*	*29*	*163*	*132*	*10*	*33*	*117*	*134*
Total percentage[j]	–	–	*8.0%*	*27.9%*	*32.2%*	*3.3%*	*7.6%*	*27.1%*	*27.9%*

NR Not reported
[a]Lumpy solids: 8, soft solids: 2
[b]Epigastric bloat
[c]Chest pain on eating
[d]Lumpy solids
[e]Only results related to 3 cm
[f]Moderate or severe
[g]Baseline sample size, no follow-up sample size presented
[h]Lumpy solids: 21, soft solids: 1, liquids: 2
[i]Difficult to belch
[j]Only studies with reported data

Table B.4 Number of clinical postoperative events at the 1-year follow-up

Study	Baseline sample size, *n*	Follow-up sample size, *n*	Odynophagia, *n*	Dysphagia, *n*	Gas bloating, *n*	Vomiting, *n*	Regurgitation, *n*	Inability to vomit/belch, *n*	Heartburn or epigastric/sternal pain, *n*
Ackroyd et al. (2004)	52	42	3	11[a]	11[b]	0	1	3	4
Baigrie et al. (2005)	84	84[c]	NR	35	NR	NR	NR	NR	NR
Blomqvist et al. (2000)	52	42	NR	10	25	NR	0	NR	2
Booth et al. (2008)	64	59	13[d]	16	11	NR	10	8	29
Chrysos et al. (2001)	24	24	NR	4	9	NR	0	NR	1
Chrysos et al. (2002)	56	56	NR	2	NR	NR	NR	NR	2
Djerf et al. (2016)	36	32	NR	NR	NR	NR	NR	17	NR
Granderath et al. (2005)	50	50	NR	2	NR	NR	2	NR	1
Guérin et al. (2007)	77	64	NR	3[e]	NR	NR	NR	2	0
Khan et al. (2009)	61	34	1	5[f]	2[b]	1	1	0	4
Laine et al. (1997)	55	18	NR	0	3	NR	NR	NR	0
Mickevičius et al. (2013[g])	38	33	NR	8	12	NR	NR	NR	6
Müller-Stich et al. (2009)	20	20	NR	0	2	NR	1	1	NR
Nakadi et al. (2006)	11	11[c]	NR	0	NR	NR	NR	NR	NR
Nijjar et al. (2010)	52	48	NR	25[h]	18[i]	NR	NR	18	5
Spence et al. (2006)	39	39[c]	7	19[h]	15[b]	2	11	NR	23
Total (n)	*771*	*656*	*24*	*140*	*108*	*3*	*26*	*49*	*77*
Total percentage[j]	–	–	*13.8%*	*22.4%*	*30.1%*	*2.6%*	*8.4%*	*16.4%*	*15.1%*

NR not reported
[a]Lumpy solids: 10, soft solids: 1
[b]Epigastric bloat
[c]Baseline sample size, no follow-up sample size presented
[d]Chest pain on eating
[e]Solids: 2, liquids: 1
[f]Lumpy solids
[g]Only results related to 3 cm
[h]Solids
[i]Abdominal bloating
[j]Only studies with reported data

Table B.5 Number of clinical postoperative events at the 5-year follow-up

Study	Baseline sample size, *n*	Follow-up sample size, *n*	Odynophagia, *n*	Dysphagia, *n*	Gas bloating, *n*	Vomiting, *n*	Regurgitation, *n*	Inability to vomit/belch, *n*	Heartburn or epigastric/sternal pain, *n*
Cao et al. (2012)	50	47	NR	NR	NR	NR	6	NR	8
Galmiche et al. (2011)	288	180	NR	20	72	NR	4	NR	47
Ludemann et al. (2004)	53	51	NR	14[a]	38[b]	NR	NR	22	5
Mickevičius et al. (2013[c])	38	29	NR	3	8	NR	NR	NR	4
Nijjar et al. (2010)	52	44	NR	18[a]	26	NR	NR	16	12
Nilsson et al. (2004)	30	17	NR	7	NR	NR	1	NR	2
O'Boyle et al. (2002)	52	50	8	16[a]	36[d]	0	5	24	24
Watson et al. (2012)	39	37	NR	26[a]	27[b]	NR	NR	15	14
Wijnhoven et al. (2008)	55	49	NR	28[a]	25[e]	NR	NR	15	20
Total (n)	*657*	*504*	*8*	*132*	*232*	*0*	*16*	*92*	*136*
Total percentage[f]	–	–	*16.0%*	*28.9%*	*52.7%*	–	*5.4%*	*39.8%*	*27.0%*

NR Not reported
[a]Solids
[b]Abdominal bloating
[c]Only results related to 3 cm
[d]Epigastric bloat
[e]Bloated/distended after eating
[f]Only studies with reported data

Table B.6 Number of clinical postoperative events at ≥ 10-year follow-up

Study	Baseline sample size, *n*	Follow-up sample size, *n*	Follow-up time	Odynophagia, *n*	Dysphagia, *n*	Gas bloating, *n*	Vomiting, *n*	Regurgitation, *n*	Inability to vomit/belch, *n*	Heartburn or epigastric/sternal pain, *n*
10 years										
Broeders et al. (2009)	98	79	10 years	NR	42	NR	NR	23	NR	32
Cai et al. (2008)	53	48	10 years	NR	25[a]	14	NR	NR	24	7
Chew et al. (2011)	55	43	10 years	3	23[b]	17	2	7	13	21
Djerf et al. (2016)	36	32	10 years	NR	NR	NR	NR	NR	29	NR
Mardani et al. (2009)	52	42	10 years	NR	7	NR	6	4	18	4
Yang et al. (2008)	52	44	10 years	3	19[c]	29[d]	1	4	18	15
Total (n)	*346*	*288*	–	*6*	*116*	*60*	*9*	*38*	*102*	*79*
Total percentage[e]	–	–	–	*6.9%*	*45.3%*	*44.4%*	*7.0%*	*18.3%*	*48.8%*	*30.9%*
>10 years										
Rudolf-Stringer et al. (2020)	53	41	15–20 yea	NR	29[a,f]	25	NR	NR	14	17[g]
Kinsey-Trotman et al. (2018)	52	39	11 years	2[h]	24[h]	14[d,h]	1[h]	2[h]	19[h]	19[h]
		30	15–20 yea	2	25[i]	15[d]	0	0	13	26
Oor et al. (2017)	98	58	17 years	NR	28	NR	4	15	NR	25
Roks et al. (2017)	84	52	12 years	NR	NR	21	NR	NR	11	NR
Salminen et al. (2012)	55	48	15 years	NR	15	NR	NR	NR	NR	NR
Total (n)	*342*	*238*	–	*2*	*97*	*61*	*4*	*15*	*38*	*68*
Total percentage[e]	–	–	–	*6.7%*	*55.7%*	*49.6%*	*4.5%*	*17.0%*	*30.9%*	*53.5%*

NR not reported
[a]Solids
[b]Lumpy solids: 17, soft solids: 3, liquids: 3
[c]Lumpy solids
[d]Epigastric bloat
[e]Only studies with reported data
[f]Sample size *n* = 38
[g]Sample size *n* = 39
[h]Not included in the total summary
[i]Solids: 16, liquids: 9

Table B.7 Number of reoperations up to 4 to 6 weeks, 6 months, 1 year, 5 years, and 10 years after operation

Study[a]	Follow-up	Baseline	4 to 6 weeks		6 months		1 year		5 years		10 years	
		Sample size	Sample size	Events	Sample size	Events	Sample size	Events	Sample size	Events	Sample size	Events
Anvari et al. (2006)	1 year	52	NR	NR	NR	NR	44	2	–	–	–	–
Aye et al. (2012)	1 year	46	NR	NR	NR	NR	46[b]	2	–	–	–	–
Baigrie et al. (2005)	2 years	84	84	0	NR	NR	NR	NR	–	–	–	–
Blomqvist et al. (2000)	1 year	52	NR	NR	NR	NR	42	3	–	–	–	–
Cao et al. (2012)	5 years	50	NR	NR	NR	NR	NR	NR	47	3	–	–
Djerf et al. (2016)	10 years	36	NR	NR	NR	NR	33	0	NR	NR	32	0
Draaisma et al. (2006a), Broeders et al. (2009)	5 years	98	NR	NR	98[b]	8	98[b]	10	79	12	–	–
	10 years	–	NR	NR	NR	NR	NR	NR	NR	NR	79	12
Draaisma et al. (2006b)	6 months	25	NR	NR	25	2	–	–	–	–	–	–
Håkanson et al. (2019)	5 years	227	227[b]	1	NR	NR	NR	NR	177	5	–	–
Khan et al. (2009)	1 year	61	NR	NR	NR	NR	34	3	–	–	–	–
Koch et al. (2013)	1 year	62	NR	NR	62	2	60	6	–	–	–	–
Laine et al. (1997)	1 year	55	NR	NR	NR	NR	18	0	–	–	–	–
Mahon et al. (2005)	1 year	109	NR	NR	NR	NR	106	4	–	–	–	–
Mickevičius et al. (2008[c]), Mickevičius et al. (2013[c])	1 year	38	NR	NR	30	0	31	2	–	–	–	–
	5 years	–	NR	NR	NR	NR	NR	NR	29	2	–	–
Müller-Stitch et al. (2007), Müller-Stitch et al. (2009)	1 month	20	20	0	–	–	–	–	–	–	–	–
	1 year	–	NR	NR	20	0	20	0	–	–	–	–
Spence et al. (2006), Watson et al. (2012)	1 year	39	39[b]	1	39	3	39[b]	4	–	–	–	–
	5 years	–	NR	NR	NR	NR	NR	NR	37	4	–	–
Watson et al. (1997), O'Boyle et al. (2002), Yang et al. (2008)	6 months	52	52[b]	4	52[b]	5	–	–	–	–	–	–
	5 years	–	NR	NR	NR	NR	52[b]	6	50	7	–	–
	10 years	–	NR	NR	NR	NR	NR	NR	NR	NR	44	8
Watson et al. (1999), Ludemann et al. (2005), Cai et al. (2008)	6 months	53	53	1	–	–	–	–	–	–	–	–
	5 years	–	NR	NR	NR	NR	53[b]	2	51	4	–	–
	10 years	–	NR	NR	NR	NR	NR	NR	NR	NR	48	6
Watson et al. (2001), Wijnhoven et al. (2008), Chew et al. (2011)	6 months	55	55[b]	6	55[b]	9	–	–	–	–	–	–
	5 years	–	NR	NR	NR	NR	55[b]	10	49	12	–	–
	10 years	–	NR	NR	NR	NR	NR	NR	NR	NR	43	14
Watson et al. (2004), Nijjar et al. (2010)	6 months	52	NR	NR	52[b]	0	–	–	–	–	–	–
	5 years	–	NR	NR	NR	NR	48	0	44	0	–	–
Wenner et al. (2001), Nilsson et al. (2004)	6 months	30	25	0	25	0	–	–	–	–	–	–
	5 years	–	NR	NR	NR	NR	25	0	24	2	–	–
Total (n)	–	*1296*	*555*	*13*	*458*	*29*	*804*	*54*	*587*	*51*	*246*	*40*
Total percentage[d]	–	–	–	*2.3%*	–	*6.3%*	–	*6.7%*	–	*8.7%*	–	*16.3%*

NR not reported
[a]Each row corresponds to the same study and population, published in one or more articles, e.g., Draaisma et al. (2006a) and Broeders et al. (2009). Number of studies for each follow-up timepoint; 4–6 weeks: 8 studies; 6 months: 10 studies; 1 year: 17 studies; 5 years: 10 studies; ≥ 10 years: 5 studies
[b]Participants at baseline. Study did not present number of participants at follow-up
[c]Results related to 3-cm wrap
[d]Only studies with reported data

Table B.8 Number of proton pump inhibitor (PPI) users at 1 year, 5 years, 10 years, and 12 to 15 years after operation

Study[a]	Follow-up	Baseline	1 year		5 years		10 years		12 to 15 years	
		Sample size	Sample size	Events	Sample size	Events	Sample size	Events	Sample size	Events
Anvari et al. (2006)	1 year	52	44	0	–	–	–	–	–	–
Aye et al. (2012)	1 year	46	46[b]	2	–	–	–	–	–	–
Roks et al. (2017)	12 years	84	NR	NR	NR	NR	NR	NR	52	4
Mardani et al. (2008)	10 years	52	NR	NR	NR	NR	42	14	–	–
Cao et al. (2012)	5 years	50	NR	NR	47	4	–	–	–	–
Djerf et al. (2016)	10 years	36	NR	NR	NR	NR	32	8	–	–
Draaisma et al. (2006a), Broeders et al. (2009)	5 years	98	NR	NR	79	11	–	–	–	–
	10 years	–	NR	NR	NR	NR	79	21	–	–
Galmiche et al. (2011)	5 years	288	NR	NR	180	29	–	–	–	–
Håkanson et al. (2019), Analatos et al. (2021)	5 years	227	215	37	NR	NR	–	–	–	–
	15 years	–	NR	NR	NR	NR	NR	NR	149	42
Laine et al. (1997)	1 year	55	18	0	–	–	–	–	–	–
Ludemann et al. (2005), Cai et al. (2008)	5 years	53	NR	NR	51	6	–	–	–	–
	10 years	–	NR	NR	NR	NR	48	9	–	–
Mickevičius et al. (2008[c]), Mickevičius et al. (2013[c])	1 year	38	31	4	–	–	–	–	–	–
	5 years	–	NR	NR	29	5	–	–	–	–
Müller-Stitch et al. (2009), Lang et al. (2022)	1 year	20	20	3	–	–	–	–	–	–
	12 years	–	NR	NR	NR	NR	NR	NR	12	4
Nijjar et al. (2010)	5 years	52	48	6	44	2	–	–	–	–
Nilsson et al. (2004[d])	5 years	30	NR	NR	22	1	–	–	–	–
O'Boyle et al. (2002), Yang et al. (2008)	5 years	52	NR	NR	50	3	–	–	–	–
	10 years	–	NR	NR	NR	NR	44	4	–	–
Watson et al. (2012)	5 years	39	NR	NR	37	3	–	–	–	–
Wijnhoven et al. (2008), Chew et al. (2011)	5 years	55	NR	NR	NR	NR	–	–	–	–
	10 years	–	NR	NR	NR	NR	43	11	–	–
Total (n)	–	*1327*	*422*	*52*	*539*	*64*	*288*	*67*	*213*	*50*
Total percentage[e]	–	–	–	*12.3%*	–	*11.9%*	–	*23.3%*	–	*23.5%*

NR not reported
[a]Each row corresponds to the same study and population, published in one or more articles. Example Håkanson et al. 2019 and Analatos et al. 2021. Not enough studies to present reliable 4–6-week and 6-month results. Number of studies for each follow-up timepoint; 1 year: 7 studies; 5 years: 9 studies; 10 years: 6 studies; 12–15 years: 3 studies
[b]Participants at baseline. Study did not present number of participants at follow-up
[c]Only results related to 3 cm
[d]Discrepancy between this 5-year sample size and the one presented for reoperation (Table 5), since sample size for reoperation needs to include the events
[e]Only studies with reported data

Table B.9 Appraisal of included studies

Study	Randomization	Allocation concealment	Baseline groups similar	Blind participants	Blind deliverers	Blind outcome assessors	Groups treated identically	Follow-up complete	Intention-to-treat analysis	Outcomes measured same	Outcomes measured reliable	Appropriate statistical analysis	Appropriate trial design	Overall appraisal
Ackroyd et al. (2004)	Unclear	Yes	Yes	No	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Anvari et al. (2006)	Yes	No	Yes	No	No	No	No	No	Unclear	Yes	Unclear	Yes	Yes	Include
Attwood et al. (2008)	Unclear	Unclear	Yes	No	No	No	No	Unclear	Yes	No	Unclear	Unclear	Yes	Include
Galmiche et al. (2011)	Unclear	Unclear	Yes	No	No	No	No	No	Yes	No	Unclear	Yes	Yes	Include
Hatlebakk et al. (2016)	Unclear	Unclear	Yes	No	No	No	No	No	Yes	No	Unclear	Yes	Yes	Include
Aye et al. (2012)	Unclear	Unclear	Yes	Yes	No	No	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Baigrie et al. (2005)	Unclear	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Roks et al. (2017)	Unclear	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Blomqvist et al. (2000)	Yes	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	No	Unclear	Yes	Yes	Include
Mardani et al. (2009)	Yes	Yes	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Booth et al. (2008)	Unclear	Yes	Yes	Yes	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Cao et al. (2012)	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Include
Chrysos et al. (2001)	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Chryearsos et al. (2002)	Yes	Unclear	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Djerf et al. (2016)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Draaisma et al. (2006a)	Unclear	Unclear	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Broeders et al. (2009)	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Include
Oor et al. (2017)	Unclear	Unclear	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Draaisma et al. (2006b)	Unclear	Unclear	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Franzén et al. (2005)	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Include
Granderath et al. (2005)	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Include
Guérin et al. (2007)	Unclear	Unclear	Unclear	Unclear	No	Yes	Unclear	No	Yes	Yes	Unclear	Yes	Yes	Include

Table B.9 (Continued)

Study	Randomization	Allocation concealment	Baseline groups similar	Blind participants	Blind deliverers	Blind outcome assessors	Groups treated identically	Follow-up complete	Intention-to-treat analysis	Outcomes measured same	Outcomes measured reliable	Appropriate statistical analysis	Appropriate trial design	Overall appraisal
Heikkinen et al. (1999)	Unclear	Yes	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Håkanson et al. (2019)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Analatos et al. (2022)	Yes	Yes	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Khan et al. (2009)	Unclear	Yes	Yes	Yes	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Koch et al. (2012)	Yes	Unclear	Yes	Unclear	No	Unclear	Yes	No	Unclear	Yes	Unclear	Yes	Yes	Include
Koch et al. (2013)	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Laine et al. (1997)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Salminen et al. (2012)	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Laws et al. (1997)	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Include
Mahon et al. (2005)	Yes	Unclear	Yes	No	No	Unclear	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Include
Mickevičius et al. (2008)	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Mickevičius et al. (2013)	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Morino et al. (2006)	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Include
Müller-Stitch et al. (2007)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Müller-Stitch et al. (2009)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	Include
Lang et al. (2022)	Unclear	Unclear	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	No	Yes	Include
Nakadi et al. (2006)	Unclear	Unclear	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Include
Paranyak et al. (2021)	Yes	No	Yes	Yes	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Patterson et al. (2000)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Include
Qin et al. (2013)	Unclear	Unclear	Yes	Unclear	No	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Include
Raue et al. (2011)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Spence et al. (2006)	Unclear	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include

Table B.9 (Continued)

Study	Randomization	Allocation concealment	Baseline groups similar	Blind participants	Blind deliverers	Blind outcome assessors	Groups treated identically	Follow-up complete	Intention-to-treat analysis	Outcomes measured same	Outcomes measured reliable	Appropriate statistical analysis	Appropriate trial design	Overall appraisal
Watson et al. (2012)	Unclear	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Strate et al. (2008)	Unclear	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Include
Wang et al. (2015)	Yes	Yes	Yes	Unclear	No	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Watson et al. (1997)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
O'Boyle et al. (2002)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Yang et al. (2008)	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Include
Kinsey-Trotman et al. (2018)	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Watson et al. (1999)	Unclear	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Include
Ludemann et al. (2005)	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Cai et al. (2008)	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Rudolph-Stringer et al. (2020)	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Watson et al. (2001)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Wijnhoven et al. (2008)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Chew et al. (2011)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Watson et al. (2004)	Unclear	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include
Nijjar et al. (2010)	Unclear	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Include
Wenner et al. (2001)	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Include
Nilsson et al. (2002)	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Include
Nilsson et al. (2004)	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Include

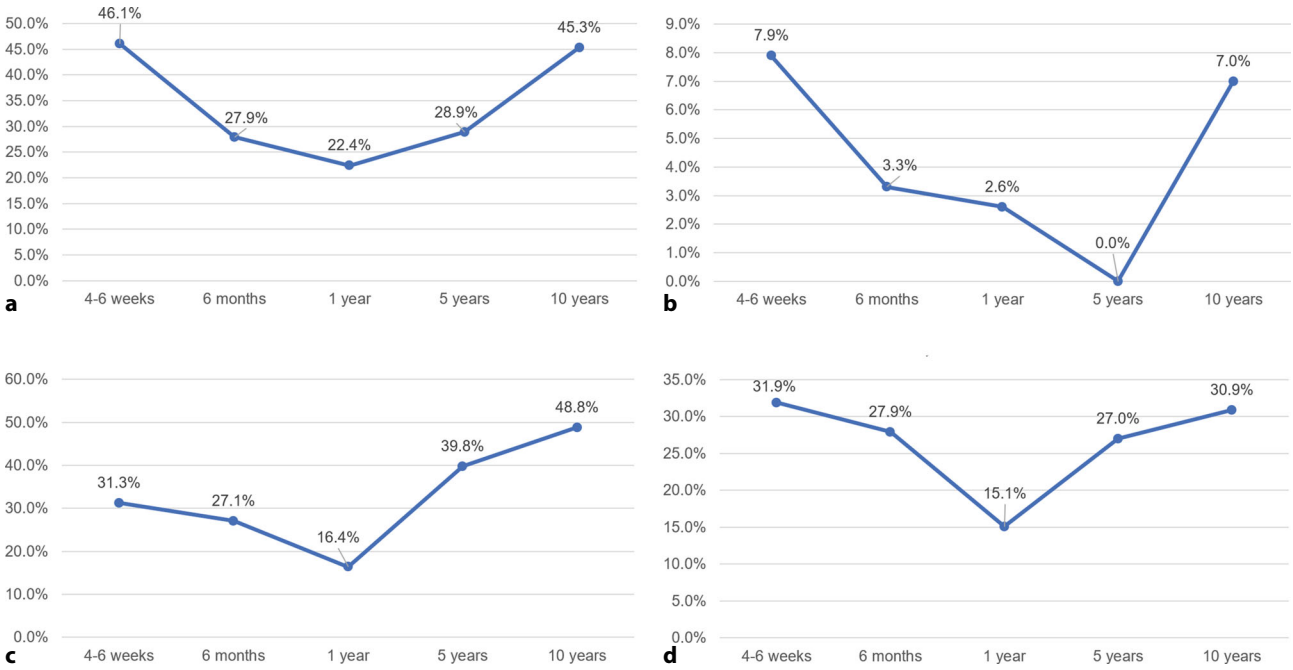

Fig. B.1 Complication rates for **a** dysphagia, **b** vomiting, **c** inability to vomit/belch, and **d** heartburn or epigastric/sternal pain

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