

Network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults

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Background: Proton pump inhibitors are the mainstay of treatment for gastro-oesophageal reflux disease, but are associated with ongoing costs and side-effects. Antireflux surgery is cost-effective and is preferred by many patients. A total (360° or Nissen) fundoplication is the traditional procedure, but other variations including partial fundoplications are also commonly performed, with the aim of achieving durable reflux control with minimal dysphagia. Many RCTs and some pairwise meta-analyses have compared some of these procedures but there is still uncertainty about which, if any, is superior. Network meta-analysis allows multiple simultaneous comparisons and robust synthesis of the available evidence in these situations. A network meta-analysis comparing all antireflux procedures was performed to identify which has the most favourable outcomes at short-term (3–12 months), medium-term (1–5 years) and long-term (10 years and more than 10 years) follow-up.

Methods: Article databases were searched systematically for all eligible RCTs. Primary outcomes were quality-of-life measures and dysphagia. Secondary outcomes included reflux symptoms, pH studies and complications.

Results: Fifty-one RCTs were included, involving 5357 patients and 14 different treatments. Posterior partial fundoplication ranked best in terms of reflux symptoms, and caused less dysphagia than most other interventions including Nissen fundoplication. This was consistent across all time points and outcome measures.

Conclusion: Posterior partial fundoplication provides the best balance of long-term, durable reflux control with less dysphagia, compared with other treatments.

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Introduction

Gastro-oesophageal reflux disease (GORD) affects up to 20 per cent of the population in the Western world¹. Proton pump inhibitor (PPI) therapy has been the mainstay of treatment for the past 20 years, with surgery reserved mainly for patients with refractory GORD². However, the cost, inconvenience and potential side-effects of long-term acid suppression mean that many patients prefer surgery^{3,4}, and several recent RCTs^{4–7} have confirmed the long-term cost-effectiveness of surgical intervention compared with

continued medical therapy. Surgical procedures for GORD largely involve the creation of a flap valve by wrapping the gastric fundus around the gastro-oesophageal junction (so-called fundoplication)⁸. Several variations of this are commonly performed, including total 360° (Nissen) fundoplication⁹, and partial fundoplication positioned either posterior or anterior to the oesophagus as it enters the abdomen via the oesophageal hiatus of the diaphragm. The aim of partial wraps is to reduce the incidence of dysphagia, but the potential disadvantage is poorer reflux control¹⁰.

More than 50 RCTs have compared various fundoplication procedures, involving thousands of patients and years of follow-up data. Although the results of many have been pooled in pairwise meta-analyses, all these have inherent limitations, as they have either combined different fundoplication techniques to allow a head-to-head analysis^{11–14}, or compared only two techniques in isolation^{3,15–17}. It therefore remains difficult, more than 40 years after the first RCT was published¹⁸, to determine which fundoplication technique is superior, both in terms of reflux control and potential harms¹⁹. Calls have been made for even more RCTs²⁰, whereas others have suggested that none of the options is ideal²¹, and the choice of procedure should simply be left to the surgeon¹⁰.

Network meta-analysis allows the simultaneous comparison of multiple different treatments for a given condition, while respecting randomization²². It can be thought of as an extension of the standard pairwise (A *versus* B) meta-analysis, to a structure that includes multiple treatments (A *versus* B *versus* C) and all the possible direct and indirect comparisons within. This increases the precision of the effect estimate, and allows valid comparisons to be made between interventions even if they have not been compared directly in an RCT²³. Network meta-analysis also enables ranking of different treatments with respect to benefits and harms.

The aim of the present systematic review and network meta-analysis was to include all available evidence from RCTs that have compared different fundoplication techniques in adults with GORD to identify which, if any, technique has the most favourable outcome profile in terms of reflux control, and side-effects such as dysphagia. As the degree of reflux control, and prevalence of dysphagia and other symptoms can change significantly over time following surgery, the analysis was repeated at four follow-up time points: 3–12 months, 1–5 years, 5–10 years and over 10 years.

Methods

This study was conducted in accordance with the Cochrane Collaboration's recommended methodology²⁴ and the PRISMA guidelines²⁵, including those specifically concerning network meta-analysis²⁶. The study protocol, including a detailed analysis plan, was prepared and published *a priori*²⁷. A complete description of the methods is included in *Appendix S1* (supporting information).

Search strategy and study selection

Article databases, trial registries and grey literature sources were searched from inception to March 2017, using a

structured search strategy (*Appendix S2*, supporting information) and no language restrictions, for RCTs comparing any surgical antireflux procedures, and/or PPIs, in adult patients with GORD. Two authors independently screened all titles and abstracts for eligibility. Selected full texts were then reviewed independently before a list of included studies was finalized, in discussion with a third author.

Outcome measures

All trials that reported the primary outcomes, including general and gastrointestinal-specific quality-of-life scores and dysphagia, were included. Trials were also included if they reported any of the following secondary outcomes: reflux symptoms, oesophageal acid exposure scores, total oesophageal acid exposure time, dilatation for dysphagia rate, reoperation rate, postoperative complications and gas bloat syndrome (*Appendix S1*, supporting information).

Data extraction and quality assessment

A structured, prepiloted electronic form was used by two authors independently to collect extracted data. Study authors were contacted to request missing data if an e-mail address was available. Data that were still missing were calculated if possible using established methodology, or imputed (*Appendix S1*, supporting information). All outcome data except postoperative complications were recorded separately in four groups according to follow-up time: 3–12 months, 1–5 years, 5–10 years and more than 10 years. Continuous (score) and dichotomous (rate) data for each outcome were both included and recorded separately. Where one trial reported the same outcome for different follow-up times, data were included in the appropriate groups, ensuring that duplication was avoided.

The Cochrane risk-of-bias tool²⁸ was used to assess the methodological quality of all included RCTs (*Appendix S1*, supporting information).

Statistical analysis

A random-effects network meta-analysis was performed using the suite of Stata[®] 13.1 routines (StataCorp, College Station, Texas, USA) available for this^{29,30} (*Appendix S1*, supporting information). The main analyses included all treatments for which data were available for that outcome and follow-up time. Fundoplications were divided into the following four groups: 90°, at least 120° anterior partial fundoplication (APF), at least 180° posterior partial fundoplication (PPF) and total 360° Nissen fundoplication (NF). Allocation of 120° APF was subjected to sensitivity

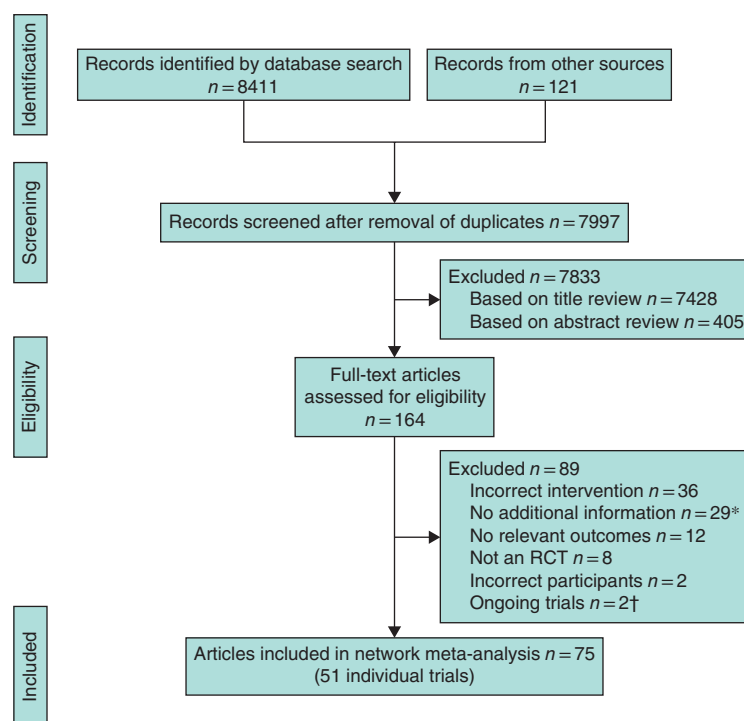


Fig. 1 PRISMA flow chart showing selection of articles for review. *Includes duplicate publications and articles reporting results for an included trial with no additional relevant data. †No data currently available from trial investigators

analysis by reallocation to the 90° group. Network maps for each outcome were produced to provide a visual summary of the network of evidence available. An intention-to-treat analysis was used.

For outcome time points with enough data available, and statistically significant differences between treatments, the ranking probabilities of each fundoplication technique (and PPI, as the reference) were calculated, and presented as a rankogram²⁹. The ranking (surface under the cumulative ranking curve, SUCRA) scores for each treatment for the most commonly reported effectiveness (reflux) and adverse (dysphagia) outcomes were then combined by time point into clustered ranking plots, to enable a simultaneous comparison of benefit and harm.

Several sensitivity analyses, and testing for evidence of data heterogeneity and publication bias were also carried out (Appendix S1, supporting information).

Results

Search results and study characteristics

The database search and study selection process are summarized in Fig. 1. Fifty-one RCTs (reported in 75 papers with eligible data) were included, involving 5357

patients and 13 different surgical procedures in addition to PPIs (Table 1). The most common comparison was NF versus PPF; NF was compared with every other fundoplication in at least three RCTs. The characteristics and relevant outcomes of each included RCT are detailed in Table S1 (supporting information), and the number of trials and patients for which data were available for each outcome and follow-up time in Table S2 (supporting information).

Fig. S1 (supporting information) summarizes the risk-of-bias assessment of the included trials, and Fig. S2 (supporting information) shows the domain assessment for individual trials, categorized by comparison. Only seven trials were judged as being at low risk of bias across all domains. Many trials did not provide details of blinding and allocation concealment, although over one-quarter were judged as well blinded.

Outcomes

Reflux

Reflux was the most commonly reported efficacy outcome (Table S2, supporting information), and was therefore substituted in place of quality-of-life scores as the main efficacy outcome. Fig. 2a and Fig. S3 (supporting information) summarize the direct evidence available at 3–12 months, for

Table 1 Summary of included trials

Trial comparison	No. of trials*	No. of patients†	Publication year‡	Trial location			
				Europe	Americas	Oceania	Asia/Africa
Nissen <i>versus</i> PPF	19	2153	1989–2015	14	2		3
Nissen <i>versus</i> APF	6	530	2004–2016	3		1	2
Nissen <i>versus</i> 90°	3	225	1989–2012	1		2	
Nissen <i>versus</i> PPI	3	803	2008–2011	2	1		
PPF <i>versus</i> APF	4	339	2007–2017	3		1	
PPF <i>versus</i> 90°	1	32	1989	1			
Nissen <i>versus</i> Angelchik	3	163	1984–1994	3			
Nissen <i>versus</i> Hill	2	132	1974–2012		2		
Nissen <i>versus</i> other§	7	706	1974–2015	4	3		
PPF <i>versus</i> FND 360°	1	252	2012		1		
NSGVD <i>versus</i> NSGVP	6	438	1999–2009	4	1	1	
Bougie <i>versus</i> no bougie¶	1	171	2000		1		
BM IV <i>versus</i> Hill	1	30	1974		1		

*Number of trials reporting this comparison. Three-arm trials are therefore included three times to account for all three direct pairwise comparisons in them. †Total number of patients randomized to each comparison. The number for whom data were reported for different outcomes at different time points varies. Patients recruited in three-arm trials are counted twice to account for the two direct comparisons each patient was involved in. ‡Year of publication of index paper in each trial; subsequent follow-up papers were included in this review, but are not included in this column. §Single trial comparisons. Other procedures include: Belsey Mark IV (BM IV), Roux-en-Y duodenal diversion, cardia calibration with posterior gastropexy, Nissen with mesh hiataloplasty, Nissen with fascial graft, fixed ‘non-deformable’ 360° fundoplication (FND), mesh hiataloplasty and cardiophrenicopexy. ¶Nissen with and without use of a bougie for calibration. PPF, posterior partial fundoplication; APF, anterior partial fundoplication; 90°, 90° fundoplication; PPI, proton pump inhibitor; NSGVD, Nissen with short gastric vessel division; NSGVP, Nissen with short gastric vessel preservation.

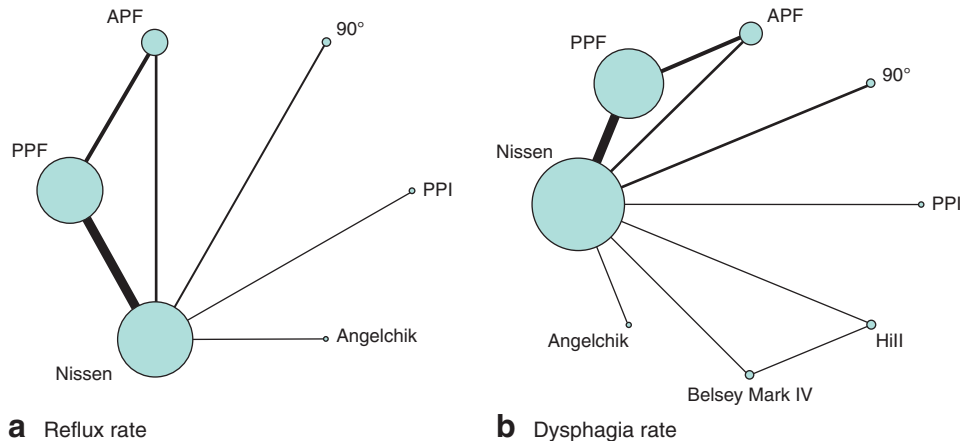


Fig. 2 Network maps of direct evidence for **a** short-term reflux and **b** dysphagia rate at 3–12 months after treatment. The size of each circle (node) is proportional to the number of patients who received the treatment. The width of the lines represents the number of RCTs that directly compared the connected pairs of treatments. PPF, posterior partial fundoplication; APF, anterior partial fundoplication; 90°, 90° fundoplication; PPI, proton pump inhibitor

rates and scores respectively. Across all time points, rate and score data showed similar overall results and rankings, despite minor variations in the treatment effect point estimates and confidence intervals.

Tables S3 and S4 (supporting information) show reflux network meta-analysis results for rate and score data

respectively. At 3–12-month follow-up, NF showed a significantly lower rate of reflux symptoms than PPI therapy or APF, and was the only fundoplication with reflux rates as low as those of the Angelchik procedure. Analysis of score data showed that all fundoplications had significantly lower reflux scores than PPI therapy, but there were no

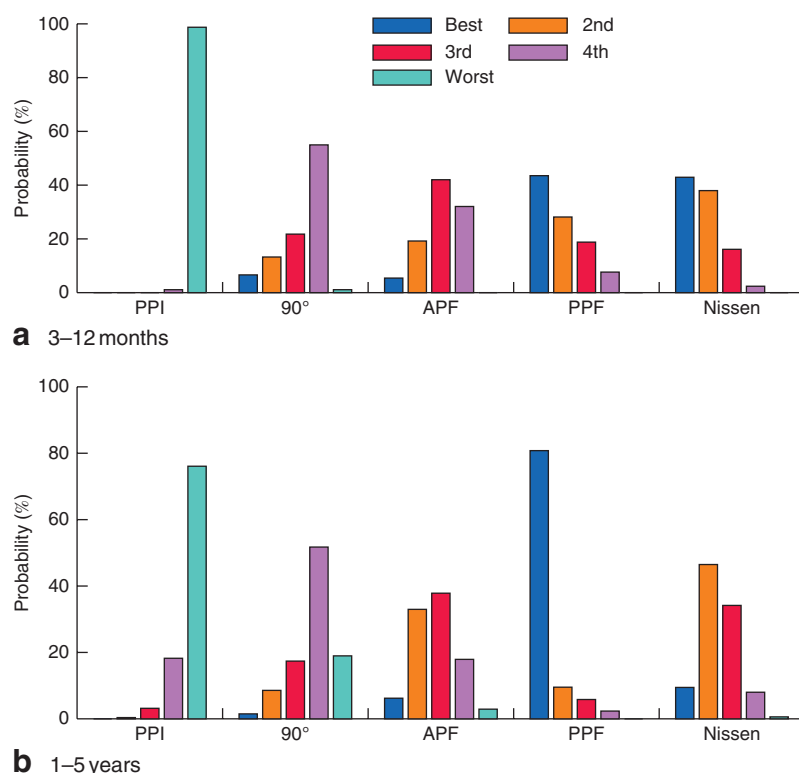


Fig. 3 Rankograms of funduplications according to reflux scores at **a** 3–12 months and **b** 1–5 years after treatment. The probability of each funduplication ranking as the best, second best, third, fourth or worst treatment in the network is shown. There were insufficient data for ranking at 5–10 years' and more than 10 years' follow-up. PPI, proton pump inhibitor; 90°, 90° funduplication; APF, anterior partial funduplication; PPF, posterior partial funduplication

statistically significant differences between the funduplications. Both NF and PPF had significantly lower reflux scores than mesh hiatoptasty with cardiophrenicopexy. *Fig. 3a* shows the funduplication rankogram for reflux scores at 3–12 months; NF and PPF ranked similarly as the best treatments, followed by APF, 90° and PPI respectively. Rate data showed similar rankings (*Fig. S4*, supporting information).

At 1–5-year follow-up, there were no statistically significant differences between the groups in the main analysis of rate data. Score data analysis showed a reduction in reflux scores with any funduplication in comparison with PPI, except 90°. PPF alone had statistically significantly lower reflux scores compared with mesh hiatoptasty with cardiophrenicopexy. Funduplication rankograms showed that PPF ranked as the best treatment (*Fig. 3b*).

At long-term follow-up, patients who underwent PPF were significantly less likely to report reflux symptoms than those who had APF or NF, although this was based on rate data from only three studies. Score data were available only for APF and NF, with no significant difference between

them. One study reported data after follow-up of more than 10 years, with no statistically significant difference in reflux rates between NF and PPF.

Pairwise meta-analysis and sensitivity analyses showed no substantive differences compared with the main analysis results (*Appendix S3*, supporting information). Apart from the 5–10-year comparison where predictive intervals were wide (suggesting significant between-study heterogeneity), there was no evidence of inconsistency or heterogeneity in the analyses.

Dysphagia

A large number of trials reported this outcome (*Table S2*, supporting information). *Fig. 2b* and *Fig. S5* (supporting information) summarize the direct evidence available at 3–12 months for rates and scores respectively. Rate and score data showed similar overall results and rankings across all time points, despite some variation in the treatment effect point estimates and confidence intervals.

Tables S5 and *S6* (supporting information) show network meta-analysis results for rate and score data

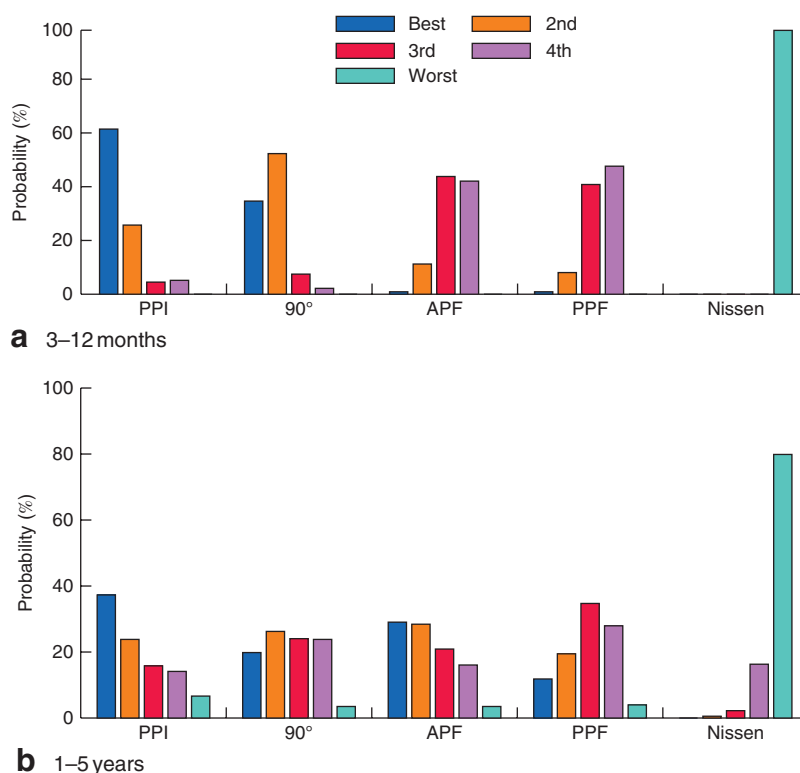


Fig. 4 Rankograms of funduplications according to dysphagia rate at **a** 3–12 months and **b** 1–5 years after treatment. The probability of each fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is shown. There were insufficient data for ranking at 5–10 years' and more than 10 years' follow-up. PPI, proton pump inhibitor; 90°, 90° fundoplication; APF, anterior partial fundoplication; PPF, posterior partial fundoplication

respectively. At 3–12-month follow-up, patients who underwent NF had a significantly higher rate of dysphagia at 3–12 months than any other group apart from Angelchik and Hill repair. NF also had significantly higher dysphagia scores than APF or 90° fundoplication. There were no statistically significant differences between the partial funduplications, or between any of them and PPI therapy. Fundoplication rankograms are shown for rate data in *Fig. 4a* and for score data in *Fig. S6* (supporting information); Nissen consistently ranked as the worst treatment, and PPF and APF ranked fairly similarly.

At 1–5 years, those who underwent any partial fundoplication were still significantly less likely to suffer from dysphagia and had lower dysphagia scores, compared with those who had NF. This is reflected in the fundoplication rankograms (*Fig. 4b*; *Fig. S6*, supporting information), with Nissen again ranking as the worst treatment.

At 5–10-year follow-up, NF was still associated with statistically significantly higher dysphagia scores than APF or PPF. Rate data analysis showed similar point estimates, but

with wider confidence intervals. One study that reported score data after more than 10 years for APF *versus* NF found no significant difference.

Results of pairwise meta-analysis and sensitivity analyses were largely similar to those of the main analysis (*Appendix S3*, supporting information). Predictive intervals for all comparisons were narrow, and inconsistency factors for all loops were small, suggesting no evidence of significant inconsistency or heterogeneity.

Quality-of-life scores

Both general (health-related) and gastrointestinal/reflux-specific quality-of-life scores were reported by a small number of trials, with all time point analyses for these two outcomes containing data from just four trials or fewer (*Table S2*, supporting information). This paucity of data led to a decision to substitute these outcomes with reflux as the main measure of efficacy in this review. Network meta-analysis results are detailed in *Appendix S3*, *Figs S7* and *S8*, and *Tables S7* and *S8* (supporting information).

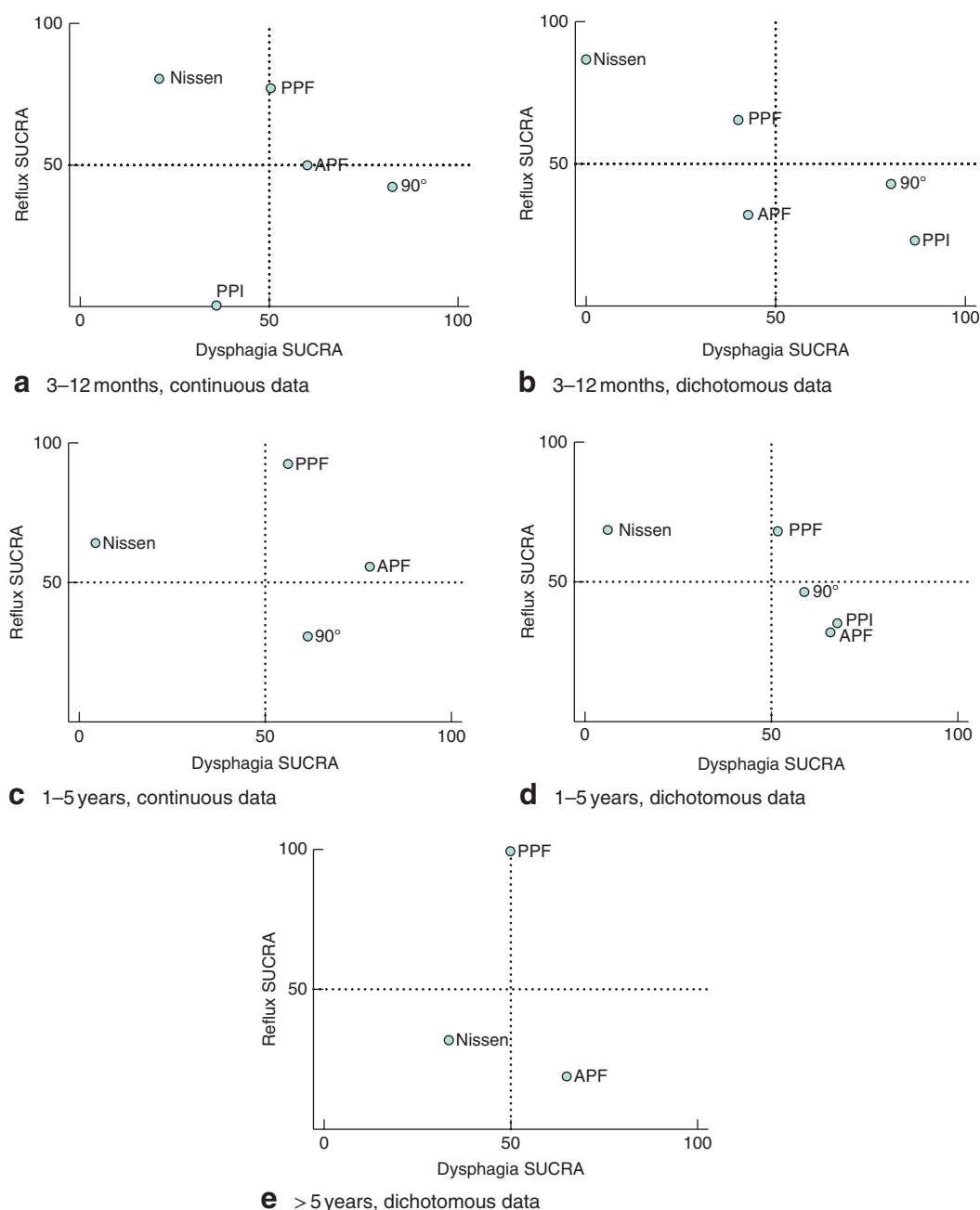


Fig. 5 Clustered ranking plots of main treatments at different time points, according to efficacy of reflux control and incidence of dysphagia: **a** 3–12-month continuous data; **b** 3–12-month dichotomous data; **c** 1–5-year continuous data; **d** 1–5-year dichotomous data; **e** more than 5-year dichotomous data. The surface under the cumulative ranking curve (SUCRA) value for each treatment is derived from the mean ranking in the network. A SUCRA value of 100 corresponds to a 100 per cent probability of that treatment ranking first for that outcome, and a value of 0 corresponds to a 100 per cent probability of that treatment ranking last. Treatments in the top right quadrant of the plot offer the best reflux control with the least dysphagia. Missing treatments indicate insufficient data to enable cluster analysis. There were insufficient continuous data beyond 5 years. Dichotomous data for the 5–10-year and over 10-year time points were combined to enable cluster analysis. PPF, posterior partial fundoplication; APF, anterior partial fundoplication; 90°, 90° fundoplication; PPI, proton pump inhibitor

Other results

The results for all other outcomes are detailed in *Appendix S3*, *Tables S9–S15* and *Figs S9–S19* (supporting information). Comparison-adjusted funnel plots, for assessment of publication bias, are shown in *Fig. S20* (supporting information). Study-specific effect sizes were distributed evenly around the pooled estimate line, with the exception of studies of NF *versus* PPF reporting reflux rate data.

Cluster plots of benefit and harm

SUCRA clustered ranking plots are shown in *Fig. 5*. Across all time points with sufficient data to enable this analysis, PPF was the only treatment that consistently ranked well in terms of reflux and dysphagia.

Discussion

This network meta-analysis has shown that PPF strikes the best balance between reflux control and side-effects including dysphagia, in comparison with other surgical procedures for GORD. PPF is also superior to medical therapy in terms of reflux control. These findings remain consistent through all follow-up time points, and different outcome measures.

Three previous pairwise meta-analyses^{3,16,17} investigated the outcomes of PPF in comparison with NF alone, concluding that PPF resulted in equivalent reflux control with less dysphagia; however, they were not able to address how other commonly performed procedures, such as APF, would compare²⁰. Other meta-analyses included PPF in a mixed 'posterior'^{12,13} or 'partial'^{11,14} fundoplication group, and compared this with a second mixed group, generating results that are difficult to interpret given the heterogeneous nature of the procedures being compared²⁰. All of the previous meta-analyses included a small number of RCTs (fewer than 12) as only direct comparisons were possible. In addition, most used only the data reported at latest follow-up from each trial, meaning that the analysis contained short- and long-term results from different patients. This introduces another source of heterogeneity, because the prevalence of symptoms such as dysphagia changes significantly over time¹⁹.

The network meta-analysis methodology used in the present study allowed much more RCT data to be included, with each procedure analysed simultaneously as a separate group in a manner that fully respects randomization²². The use of all available direct and indirect evidence increased the precision of the effect estimates. Analysing data from different follow-up times separately also

eliminated an important source of heterogeneity, and allowed outcome measures over time to be determined. These features increase the external validity and clinical applicability of the results, in comparison with other reviews.

Patient-reported scores were used to assess all primary and several secondary outcomes in this review to enable a pragmatic evaluation of the procedures⁴. More objective tools such as pH monitoring and oesophagoscopy have traditionally been regarded as the standard methods of assessing reflux control after surgery for GORD¹⁸, and manometry and mechanical studies have been used to assess side-effects such as dysphagia³¹. However, there is evidence that the results of such investigations correlate poorly with clinical outcome following surgery^{6,32–35}. Furthermore, patients who feel well after surgery with no significant symptoms are less likely to consent to further invasive tests, which may bias the results³⁶.

The best measure of surgical success is relief of symptoms without significant side-effects, as reported by the patient, particularly as the indication for antireflux surgery is usually patient preference and symptom severity³⁵. Patient-reported symptom scores have been shown to correlate best with the actual outcome as perceived by the patient³⁷.

This study has some potential limitations. The quality of included trials in any meta-analysis affects the validity of its results, and the risk of selection and performance bias in a proportion of included RCTs was assessed as unclear or high, as blinding was not attempted or reported. Blinding was not possible in trials that compared surgical intervention with PPI therapy. Overall, trial quality did not significantly vary between comparisons, and there was no evidence of systematic publication bias.

The inclusion of non-fundoplication procedures, one of which is no longer performed because of safety concerns³⁸, may be questioned. This was done to enable use of indirect evidence available from those RCTs, and therefore increase the precision of the overall effect estimates. Furthermore, each of these older procedures was analysed as a separate individual node in all analyses, and subjected to sensitivity analysis (by exclusion) to ensure that its inclusion did not influence the main findings.

Current US¹⁰ and European¹⁹ guidelines suggest that the choice of antireflux procedure should be left to the individual surgeon according to their expertise and regional practice, as the conclusions of published trials and reviews have been mixed. This network meta-analysis, which incorporates the results of over 50 RCTs involving more than

5300 patients, has shown that PPF provides the best balance of reflux control and dysphagia, in comparison with all other antireflux procedures and medical therapy, and that this effect is durable.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.