Advanced Meta-analysis in Surgical Research

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Abstract

The continuous development and refinement of techniques is a key attribute of the discipline of surgery. Robust evidence derived from randomised clinical trials and subsequent synthesis using meta-analysis methods is therefore an indispensable tool in modern evidence-based surgical practice. This thesis aimed to address two challenges to the development of this evidence, namely the synthesis of trial data where multiple treatment comparisons exist, and the influence of sources of bias on the results of surgical randomised trials.

Research synthesis typically employs pairwise meta-analysis methods to summarise trial data. However, there are more than two treatment options available for most conditions, meaning that data pertaining to all treatments cannot be incorporated using pairwise methodology. Network meta-analysis allows for the simultaneous comparison of multiple treatments and enables their ranking in terms of benefit and harm. This thesis used two different examples to explore this method's utility in surgical research synthesis.

Firstly, network meta-analysis methodology was used to investigate the efficacy of preoperative carbohydrate loading for patients undergoing elective surgery. None of the previously published pairwise meta-analyses had been able to account for the different doses and control treatments used in trials. This network meta-analysis represents the most comprehensive synthesis of the available evidence, and showed that carbohydrate loading confers a small reduction in length of stay when compared to fasting, but no significant difference when compared to water or placebo, and no other clinically important effect on postoperative outcomes.

Secondly, all described anti-reflux operations were assessed and ranked using network meta-analysis methods to summarise the entirety of available randomised trial data, to determine the optimal procedure for the treatment of gastro-oesophageal reflux disease. This had remained an unresolved question despite numerous pairwise meta-analyses. The results showed that a posterior partial fundoplication provides the best balance of long-term, durable reflux control with less dysphagia, compared to other treatments.

The second half of this thesis explored the effect of non-blinding and other methodological deficiencies on surgical trials. Recent pooled studies have provided empirical evidence that

these potential sources of bias significantly influence reported trial results by exaggerating the effect estimate of the studied treatment. Surgical randomised trials have important differences to drug trials, and it is important to determine whether this effect also applies to them. A study using meta-epidemiological methods at an individual trial level was conducted to determine how lack of bias-minimisation measures including blinding affects the reported outcomes of surgical randomised trials, using data from over 300 trials. The results showed that trials that did not use blinding or adequate random sequence generation reported a significantly greater difference between treatment groups compared to trials that used such measures.

This thesis has demonstrated the utility of network meta-analysis in surgical research synthesis, and produced definitive evidence-based answers to two questions. Many more clinically relevant questions can be answered in future using the same methods. This thesis has also empirically proven the importance of implementing blinding in surgical trials, which is relevant for appraising published trials and designing future randomised trials.

Acknowledgements

Whoever does not thank others, does not thank God – Hadith.

During the course of a five year project such as this with its highs and lows, there is a risk of losing track of all the people one is indebted to. The following words are not meant to be exhaustive, but my hope is that they will go some way towards documenting my real sense of gratitude and appreciation to everyone who has helped, supported and encouraged me on this incredible journey.

I would not have even embarked on this project without Professor John McCall's sincere encouragement. I will never forget that afternoon in late 2012 when we sat down to discuss potential topics, and Prof enthusiastically took to the whiteboard with a marker and drew out a network map, telling me that if he was in my shoes he would be definitely doing this project. I think he said this only because my reticence at the time was unfortunately obvious, and I cannot express how grateful I am for his sincerity, and for agreeing to be my primary supervisor. But that was only the beginning. Before this PhD journey I had heard from many colleagues about different supervisor styles and levels of support, but Prof has been nothing short of phenomenal and his support has been well beyond anything I have heard or expected. Always available. Always honest and sincere. Always happy to chat. Always bending over backwards to help, no matter how busy he might be. Always concerned about my personal wellbeing just as much as about the project. The list goes on and on and on. I feel truly privileged to have been supervised by Prof McCall, and I hope he does not mind me continuing to call upon him as a highly regarded mentor.

When Mr Mark Smith told me at the start of my PhD that he had never co-supervised a PhD student before, I wasn't sure what to make of it. Having worked for him clinically though, I knew that his standards were very high. What I had not realised however was the extent to which he was prepared to go out of his way to fulfil his supervisory role. Despite having to go through considerable challenges, he maintained the same level of support and supervision throughout the duration of my PhD, with exceptional clarity, wit and foresightedness. His response to my first email outlining this project, quipping that it was enough work to keep me busy for a decade, was a typical gem, and as usual, proved correct. His heartfelt messages after the terrible event on 15 March also stood out for me from among the dozens I received. I am

truly grateful for all of Mark's support and advice, and am humbled to be able to count him among my senior colleagues.

To say that Professor Peter Herbison's co-supervision, patient teaching, gentle guidance and expert statistical support was indispensable to this project would be an understatement. The Health Research Council funds he held made sure I did not have to worry about securing funds for this PhD beyond my stipend. Prof was always just an email away, and even when I felt that I had managed to come up with the worst possible way to explain a statistical problem, his responses were always quick, to the point and delightfully easy to follow.

No work of this magnitude would be possible without the help of research assistants. I really don't know how I could have finished this project without the assistance of Sam Grainger, Choo Khoo and Peter McCall. Their tireless hard graft and meticulous attention to detail were exemplary.

Any busy workplace like the Department of Surgical Sciences needs an efficient, organised, approachable and highly conscientious administrator in order to ensure all matters run smoothly. Pauline Ellwood is not just a great example of such a capable secretary, she also has the rare ability to make administrative matters seem simple and intuitive. I genuinely lost count of the number of times she did a favour for me (usually at ridiculously short notice), but one instance I will never forget: securing the required signatures on a Royal Australasian College of Surgeons scholarship application one day before it was due in the College offices in Melbourne, realising this was the case and calling the College office to check that they will accept the application even though it may arrive a day after it was due, arranging an urgent international courier to pick up the application within half an hour, then casually informing me later that it was all sorted. That application was successful, and I am truly grateful for Pauline's efforts which were truly above and beyond that afternoon, and on every other occasion I arrived unannounced at her office with a problem that needed sorting.

I suspect that my departmental advisory committee, which included Associate Professor Mark Thompson-Fawcett (chair) and Mr John Woodfield in addition to my supervisors, did not expect to have to hold regular progress meetings for five years when first approached by Prof McCall. Arranging Skype meeting at a time that suited everyone meant that they all had to compromise a bit, and often attend these meetings after hours, which I am grateful for. MTF's realistic take on timelines and progress was always grounding, and John's inquisitive, probing

approach to discussion opened up new perspectives on the methods and results on a regular basis.

I would like to acknowledge the financial support I received through PhD scholarships from the Royal Australasian College of Surgeons and the Dunedin School of Medicine. I am also very grateful to the New Zealand Board in General Surgery for their unwavering support, even as the requests for extensions and interruption of training kept coming.

I am grateful to Glenys Taylor, the Department's Finances administrator, for her help in preparing and deciphering accounting gobbledygook in grant applications and all costing and funding matters.

My thanks to Dr Vanessa Jordan and Richard German for their expert assistance in checking and refining the search strategies developed as part of this project. I am also very grateful to the Interloans staff at the University of Otago Library and the staff at the RACS Library for retrieving increasingly obscure and impossible-to-find papers for me from all corners of the globe, in all languages. It is testimony to their dedication and expertise that the total number of articles excluded from any of the reviews in this thesis because they could not be retrieved was zero. Simply amazing.

I would also like to thank Matthew Versteeg, Dr Kate Thomas, Soo Lee and Annie Stevenson with whom I shared our office (439) in the Department, for the many interesting conversations, and for putting up with my impromptu office meetings and Skype calls. I am also grateful to all the rest of the Department of Surgical Sciences for their genuine interest and stimulating discussion of this work in seminars and presentations.

I returned to full-time clinical work in June 2017 with some trepidation, as I had no idea whether my clinical colleagues would help me find enough time during and after the working day to continue making solid progress on this project. I need not have worried. All the registrars and consultant supervisors I have worked with in Dunedin and Christchurch Hospitals' Departments of General Surgery over the last five years have been very understanding and genuinely supportive. To each and every one of them – thank you.

I sometimes joke that I have a chronic family history of medicine, given that both my parents and all my siblings are also medical doctors in various specialties. One advantage though is

that they all understand first-hand the nature and stresses of clinical practice, as well as the demands of research. Their support through this project, just as much as it was before and will be in future, has been incredible. They have all helped pick me up in the lows when there seemed to be no end in sight, and celebrated my milestones and awards as if they were their own. My sincere gratitude, appreciation and thanks to my father Ashraf, and my siblings Aya, Mahmoud and Mostafa.

But of all the people I am grateful to, there are certainly none I am more indebted to than my mother Mona. In the course of my life, and particularly over the last five eventful years, she has remained my unflinching rock. There have been numerous times when things became “a bit much” (the last five years have seen me go through a marriage, the birth of my son, a divorce, two house moves, a move to Christchurch, and the loss of several friends and acquaintances in a mass shooting), and it is only because of God’s Grace, then her loving support, sage advice, words of wisdom and enveloping warmth that I have been able to pick myself up each time and keep going. I will remain completely unable to repay any of her favours upon me, and I pray for her health and happiness.

List of Awards, Grants and Presentations

The following awards, grants and presentations all relate directly to the author and the work completed within this thesis. Published Journal articles are listed separately in Appendix A.

Awards

2019 **- General Surgery Section Prize, Royal Australasian College of Surgeons 88th Annual Scientific Congress, Bangkok, Thailand.**

Best research paper presented in the General Surgery Section. Value: AUD$500.

2018 **- The Louis Barnett Prize, Royal Australasian College of Surgeons New Zealand Annual Scientific Meeting, Queenstown, New Zealand.**

Best research abstract and presentation by a New Zealand based trainee or fellow. Value: NZ$2500.

- Travel Grant Award, Royal Australasian College of Surgeons 55th Surgical Research Society Meeting, Sydney, Australia.

For oral presentation. Value: AUD$750.

- Best Oral Presentation by a Trainee Enrolled in a Higher Degree, **New Zealand Association of General Surgeons Conference, Paihia, New Zealand.**

Value: NZ$700.

- Commendation, 245th Meeting of the Otago Medical School Research Society, Dunedin, New Zealand.

For oral presentation.

- Best Oral Presentation by a Registrar, General Surgical Study Day, Christchurch, New Zealand.

Value NZ$500.

2015 **- The Young Investigator Award, 52nd Surgical Research Society Meeting, Royal Australasian College of Surgeons, Sydney, Australia.**

Best oral presentation. Value: AUD$4,000 to go towards sponsorship to attend and present at the Association of Academic Surgeons/Society of University

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PhD stipend scholarship for 2016. Value: NZ$55,000.

2014 **- Foundation for Surgery New Zealand Scholarship, Royal Australasian College of Surgeons.**
PhD stipend scholarship for 2015. Value: AU$66,000.

2013 **- Dunbar Research Scholarship, Dunedin School of Medicine, University of Otago.**
PhD stipend scholarship for 2014. Value: NZ$55,000.

Published Conference Abstracts, and Oral Presentations

International

Amer, MA, Herbison GP, Smith MD, Grainger SH, Khoo CH and McCall JL. (2019). Bias in surgical randomised trials: a meta-epidemiological study using laparoscopic versus open surgery as an example. In: Proceedings of the 88th Annual Scientific Congress of the Royal Australasian College of Surgeons, Bangkok, Thailand. ANZ J Surg *89(S1):57.*

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Amer M, Smith M, Khoo C, Herbison P and McCall J. (2018). Systematic review and network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults. In:

Proceedings of the 87th Annual Scientific Congress of the Royal Australasian College of Surgeons, Sydney, Australia. ANZ J Surg *88(S1):216.*

Amer MA, Smith MD, Khoo CH, Herbison GP and McCall JL. (2017). Systematic review and network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults. Oral presentation at the 54th Annual Surgical Research Society Meeting, Royal Australasian College of Surgeons, Adelaide, Australia.

Amer MA, Smith MD, Herbison GP, Plank LD and McCall JL. (2017). Preoperative carbohydrate loading and recovery after surgery – a multiple treatments meta-analysis. Invited oral presentation at the 12th Annual Academic Surgical Congress, Association for Academic Surgery, Las Vegas, Nevada, USA.

Amer MA, Smith MD, McCall JL and Herbison GP. (2015). Preoperative carbohydrates for enhancing recovery after elective surgery: a multiple-treatments meta-analysis. Oral presentation at the 52nd Annual Surgical Research Society Meeting, Royal Australasian College of Surgeons, Sydney, Australia.

National

Amer MA, Herbison GP, Smith MD, Grainger SH, Khoo CH and McCall JL. (2018). Bias in surgical randomised trials: a meta-epidemiological study using laparoscopic versus open surgery as an example. Oral presentation at the New Zealand Annual Surgical Meeting, Royal Australasian College of Surgeons, Queenstown, New Zealand.

Amer MA, Smith MD, Khoo CH, Herbison GP and McCall JL. (2018). Systematic review and network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults. Oral presentation at the New Zealand Association of General Surgeons Conference, Paihia, New Zealand.

Amer MA, Smith MD, McCall JL and Herbison GP. (2015). Preoperative carbohydrates for enhancing recovery after elective surgery: a multiple treatments meta-analysis. Oral presentation at the New Zealand Annual Scientific Meeting of the Royal Australasian College of Surgeons, Queenstown, New Zealand.

Regional/Local

Amer MA, Herbison GP, Smith MD, Grainger SH, Khoo CH and McCall JL. (2018). Bias in surgical randomised trials: a meta-epidemiological study using laparoscopic versus open surgery as an example. Oral presentation at the General Surgical Study Day, Christchurch, New Zealand.

Amer MA, Herbison GP, Smith MD, Grainger SH, Khoo CH and McCall JL. (2018). Bias in surgical randomised trials: a meta-epidemiological study using laparoscopic versus open surgery as an example. In: Proceedings of the 245th meeting of the Otago Medical School Research Society, Dunedin, New Zealand. NZMJ *in press.*

Amer MA, Smith MD, McCall JL and Herbison GP. (2015). A systematic review and multiple treatments meta-analysis to evaluate preoperative carbohydrate loading. Oral presentation at the Inaugural Dunedin School of Medicine Symposium, Dunedin, New Zealand.

Amer MA, Smith MD, McCall JL and Herbison GP. (2015). A systematic review and multiple treatments meta-analysis to evaluate preoperative carbohydrate loading for enhancing recovery after elective surgery. In: Proceedings of the 231st meeting of the Otago Medical School Research Society, Dunedin, New Zealand. NZMJ *128(1425):6740.*

A total of eleven Departmental presentations and seminars were also delivered between 2014 and 2018, covering various components of this thesis, to the Department of Surgical Sciences, Dunedin School of Medicine; the Department of Women's and Children's Health, Dunedin School of Medicine; the Dunedin Hospital Medical Forum; and the Department of General Surgery, Christchurch Hospital.

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ABBREVIATIONS

90º or 90 deg	90 degree fundoplication
APF	Anterior partial fundoplication
ASA	American Society of Anesthesiologists
BM IV	Belsey Mark IV
CABG	Coronary artery bypass grafting
CENTRAL	Cochrane Central Register of Controlled Trials
CHO	Carbohydrate
CI	Confidence interval
CLEAR	Critical Literature Evaluation and Research
CONSORT	Consolidated Standards of Reporting Trials
Cont	Continuous (score) data
Dich	Dichotomous (rate) data
DMS	DeMeester score (oesophageal acid exposure)
DSMD	Difference in standardised mean differences
ERAS	Enhanced recovery after surgery
FND 360º	Fixed 'non-deformable' 360º fundoplication
GBS	Gas bloat syndrome
GORD	Gastro-oesophageal reflux disease
GQOL	Gastrointestinal, or reflux disease-specific quality of life score
HOMA-IR	Homeostatic model assessment of insulin resistance
IV	Intravenous
MA	Meta-analysis
MD	Mean difference
MHWC	Mesh hiatoplasty with cardiophrenicopexy
NF	Nissen fundoplication
NMA	Network meta-analysis
NR	Not reported
NS	Not specified
NSGVD	Nissen with short gastric vessel division
NSGVP	Nissen with short gastric vessel preservation
pH<4	Total oesophageal acid exposure time (percentage time pH < 4)
PPI	Proton pump inhibitors

PPF	Posterior partial fundoplication
QOL	Quality of life score
RACS	Royal Australasian College of Surgeons
RCT	Randomised clinical trial
REY	Roux-en-Y
ROR	Ratio of odds ratios
SD	Standard deviation
SGVD	Short gastric vessel division
SGVP	Short gastric vessel preservation
SMD	Standardised mean difference
SUCRA	Surface under the cumulative ranking curve

CHAPTER ONE

Introduction – Evidence-based practice, research synthesis and trial design

1.1 Evidence-based practice

The development of surgical practice and expansion of its boundaries over the past 50 years has been extraordinary (Barkun et al., 2009; Meakins, 2009). Today, there are more major surgical operations performed than childbirths worldwide (Ashrafian et al., 2009), and surgery is a substantial contributor to improved health and wellbeing. Doing so efficiently and reliably requires practice that is informed by robust scientific evidence (Meakins, 2006; Rothenberger, 2004).

Evidence-based practice aims to provide patients with the best treatment, based on scientific data derived from clinical trials. The randomised clinical trial (RCT) is the gold standard method of assessing the benefits and harms of healthcare interventions (Gattellari et al., 2001; Hrobjartsson et al., 2012), as it is the only trial design that accounts for unknown confounders (Lombardi, 2014). High quality evidence derived from these trials can guide health policy and clinical decision-making, and provide a high standard of care for patients (Potter et al., 2014), by recommending the best available interventions and treatments (Vecht et al., 2009).

The evaluation of a new procedure or treatment however may not be complete after just one or two RCTs. Different patient populations, healthcare environments and standard (control) therapies need to be accounted for by conducting multiple RCTs assessing the same treatments in different settings. The results of these trials are often variable due to factors including the setting, patient numbers, the control treatment, the outcomes of interest and the follow-up period. This leads to the publication of many papers addressing the same or a similar question with the same trial design (RCT), but with different results and conclusions. It can therefore become difficult, if not impossible, to assimilate these findings to derive an objective, evidence-based summary and recommendation without further statistical synthesis (Mant, 1999). This problem is compounded by the contemporary ‘epidemic of evidence’ (Jackson, 2018), the number of novel interventions being assessed at any one time and the rapid pace of development.

1.1.1 A brief history

The need for an objective, structured approach to synthesis of trial results to guide evidence-based practice and enable prompt introduction of proven treatments was recognised decades ago, as individual clinicians do not have the time or resources required to do this themselves (Rothenberger, 2004; Sackett et al., 1996; Sauerland et al., 1999). Archibald Cochrane (1909 – 1988), a Scottish epidemiologist, penned this need in the form of a challenge facing the medical profession in his seminal work *Effectiveness and Efficiency, Random reflections on health services* (Cochrane, 1972). He and others argued that this need was urgent because of the difficulties clinicians faced in remaining up-to-date with a burgeoning number of clinical trials, which meant that proven effective treatments were not being adopted quickly enough while less effective or less safe treatments continued to be used (Abraham, 2006). There were also increasing calls for the need to honour the very reasonable expectation of clinical trial participants, that their contribution to medical knowledge is not wasted (Chalmers et al., 2013; Naylor, 1997).

Prenatal steroid administration to premature infants to accelerate foetal lung maturation is perhaps one of the best examples of the need for prompt synthesis of accumulating RCT data, in order to achieve timely dissemination and implementation of evidence into clinical practice. An Auckland Professor of Obstetrics, Graham Liggins, began investigating preterm labour in sheep in 1959. He co-incidentally found that in-utero corticosteroid administration accelerated lung maturation (Reynolds and Tansey, 2005) and subsequently conducted an RCT on human babies in collaboration with a Paediatrician, Ross Howie, which showed a significant reduction in respiratory distress syndrome in preterm infants who received prenatal steroids (Liggins and Howie, 1972). Despite this, uptake of this simple and effective treatment was virtually non-existent, as most research at the time was focussed on preventing preterm labour, rather than managing it (Reynolds and Tansey, 2005). Subsequent RCTs published by other groups showed similar results, and these were included in reviews as early as 1981 (Crowley, 1981). However, even by 1990 less than 20% of preterm infants outside Australia and New Zealand were receiving prenatal steroids. Routine administration in the UK only became a reality in the late 1990s (Reynolds and Tansey, 2005), almost three decades after the first RCT and more than fifteen years after the first narrative review promoting its use. A cumulative meta-analysis (Sinclair, 1995) around this time demonstrated that the RCTs published after the initial studies had not changed the overall effect estimate or the confidence intervals to any major extent. Thus, these additional

trials were unnecessary, and thousands of infants were needlessly randomised to placebo instead of receiving a proven treatment. Timely synthesis and dissemination of the accumulating RCT evidence would have profoundly decreased premature infant mortality rates worldwide.

1.1.2 The Cochrane Collaboration

These calls and examples led to the founding of an international body to champion healthcare research synthesis, standardise the methodology, and promote the timely dissemination and implementation of high quality evidence into clinical practice.

In 1992, a group of Oxford clinicians and epidemiologists led by Sir Iain Chalmers established the Cochrane Centre to prepare and promote systematic reviews on obstetric healthcare, and named in honour of Archibald Cochrane who had died four years earlier. A year later, the Cochrane Collaboration was launched, and it is now the largest international organisation of its kind (Green and McDonald, 2005). Its logo incorporates a meta-analysis of the first seven RCTs investigating steroid administration to premature babies (Reynolds and Tansey, 2005), as a poignant reminder of the importance of research synthesis and evidence-based practice. The Collaboration now has over 38,000 contributors from more than 130 countries (Cochrane.org, 2018a), working in 50 review groups responsible for preparing and maintaining systematic reviews within specific healthcare areas, and supported by Methods groups, Cochrane Centres and Fields (Higgins and Green, 2011). The Collaboration maintains the Cochrane Library including the Cochrane Database of Systematic Reviews, which is one of the most widely used evidence-based practice resources worldwide. The freely available Cochrane Handbook (Higgins and Green, 2011), and RevMan (Nordic Cochrane Centre, Copenhagen), a review management and meta-analysis software package, are also produced by the Collaboration.

1.1.3 Systematic reviews and meta-analysis

A systematic review collates all empirical evidence in order to answer a specific research question. It uses explicit systematic methods designed to incorporate all relevant data and minimise bias, thus providing findings from which conclusions can be drawn, and evidence-based recommendations and decisions made (Oxman and Guyatt, 1993). The key characteristics of a well-designed systematic review include predefined eligibility criteria for studies, a systematic search of databases and trial repositories for all potentially relevant studies, explicit and

reproducible methods, an assessment of the quality of available evidence, and finally a systematic presentation and synthesis of the findings of the included studies, usually using meta-analysis (MA) methodology if appropriate (Higgins and Green, 2011).

Pairwise MA is the statistical combination of results from two or more separate studies (Glass, 1976) comparing an experimental intervention with a control, or comparing two experimental interventions (Higgins and Green, 2011). This provides a more precise estimate of the effects of a healthcare intervention by pooling the study population and therefore increasing power. MA also allows the consistency of effects across studies to be investigated, as well as the heterogeneity or differences between them, thereby helping settle controversies arising from apparently conflicting studies (Higgins and Green, 2011; Lau et al., 2006). MA is therefore a powerful tool that can help answer the research question posed in a systematic review (Salanti et al., 2008a). International guidelines groups have produced consensus statements detailing the appropriate conduct and reporting of systematic reviews and meta-analyses of healthcare interventions (Moher et al., 2009; Shamseer et al., 2015).

It is important to note that pairwise MA, like any statistical method, can be misused, leading to invalid or clinically meaningless results. Statistically combining the results of primary studies may not always be possible or appropriate, such as in the presence of considerable population, methodological or statistical heterogeneity, or when there is evidence of significant publication or reporting bias in the primary studies (Higgins and Green, 2011). This highlights the importance of combining specific subject and methodological expertise for the conduct of MA.

1.1.4 Limitations of pairwise meta-analysis

Pairwise MA is used to combine studies comparing two interventions, but for many healthcare interventions there may be more than two treatment options; each with a unique profile of risks and benefits. Research synthesis should ideally incorporate all available data pertaining to all available treatments (Song et al., 2009), but this cannot be achieved with pairwise MA where only two interventions (or one intervention and placebo) can be analysed simultaneously (Brown et al., 2014).

Systematic reviewers have traditionally tried to circumvent this problem by employing one of two strategies (Salanti et al., 2008a). The first is to select two interventions for a given condition, subject the relevant RCTs to MA, then compare the findings with other MAs that have investigated the other available interventions. This frequently produces confusing conclusions as each MA uses different study selection criteria, outcome measures and follow-up time points. One such example is encapsulated in the title of an overview of antipsychotic drugs: "Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine" (Heres et al., 2006). Another example is a review of different methods of earwax removal, which reported that "…cerumol, sodium bicarbonate, olive oil and water are all more effective than no treatment, triethanolamine polypeptide is better than olive oil, wet irrigation is better than dry irrigation, sodium bicarbonate drops followed by irrigation by nurse is more effective than sodium bicarbonate drops followed by self-irrigation, softening with triethanolamine polypeptide and self-irrigation is more effective than self-irrigation only, and endoscopic de-waxing is better than microscopic de-waxing" (Clegg et al., 2010). The aim of research synthesis is to produce succinct, clinically applicable conclusions based on available data; which cannot be easily achieved by examining multiple pairwise MAs. Another strategy is to pool the multiple interventions into two groups and perform a pairwise MA comparing them. Examples include grouping surgical or medical interventions together (Ma et al., 2012; Peters et al., 2009), or combining placebo with no intervention (Awad et al., 2013). Although the conclusions of such reviews appear more succinct than those produced by the alternate strategy discussed earlier, this approach risks "combining apples with oranges" (Higgins and Green, 2011) as there is an assumption that different interventions can be regarded as identical. The results are therefore clinically less meaningful, and important differences in effect within each group are obscured.

An alternate statistical method that simultaneously compares multiple interventions is therefore needed, in order for research synthesis to remain clinically relevant, and evidence-based practice to remain a realistic goal (Caldwell et al., 2005).

1.1.5 Network meta-analysis

Network meta-analysis (NMA) (Lumley, 2002), also called mixed treatment comparison meta-analysis or multiple treatments meta-analysis (Salanti, 2012), is an extension of the standard pairwise (A vs. B) meta-analysis to a structure that includes multiple treatments (A vs. B vs. C)

and all the possible direct and indirect comparisons within (Figure 1.1), while fully respecting randomisation (Caldwell et al., 2005; Lu and Ades, 2004). A major advantage of NMA over pairwise MA is the ability to simultaneously compare multiple treatments for a given condition, and rank those treatments in terms of their benefit and harm (Caldwell et al., 2012; Lu and Ades, 2004; Riley et al., 2017). This is particularly useful in situations where there is not enough direct evidence available (Song et al., 2009), where all possible comparisons have not been made in RCTs (Mills et al., 2013) or where RCTs have used different control treatments (Higgins and Welton, 2015). NMA also increases the precision of the effect estimate of each comparison within the network by incorporating indirect evidence, and therefore more data (Caldwell et al., 2005).

Formulae for NMA have been developed and validated using both Bayesian and frequentist statistical approaches (Caldwell et al., 2005; Franchini et al., 2012; Hutton et al., 2014; Lu and Ades, 2004). The resulting routines have become available across multiple software platforms (Bafeta et al., 2014; Brown et al., 2014; Efthimiou et al., 2016; Viechtbauer, 2010). The routine package developed by Georgia Salanti and co-workers (Chaimani et al., 2013; Chaimani and Salanti, 2015) based on Stata (StataCorp LP., College Station, Texas) utility commands (Harris et al., 2008; White, 2009, 2011) is widely used. It is also one of the packages recommended for use by the Cochrane Methods Group (Cochrane.org, 2018b). As with pairwise MA, there are international consensus guidelines on the conduct and reporting of systematic reviews which include NMA (Hutton et al., 2015).

1.1.6 Important considerations in NMA

As NMA can be considered an extension of pairwise MA (Jansen et al., 2008), the underlying principles of MA apply, but to a greater extent (Song et al., 2009). There is an assumption that RCTs of different treatment comparisons are essentially similar in all ways other than the interventions being compared (Higgins and Green, 2011). All included RCTs should therefore have sufficient methodological, population and statistical similarity to allow for a valid synthesis (Mills et al., 2013). The influence of any potentially significant differences should be checked and tested using subgroup, or sensitivity (exclusion of those studies) analysis (Donegan et al., 2010).

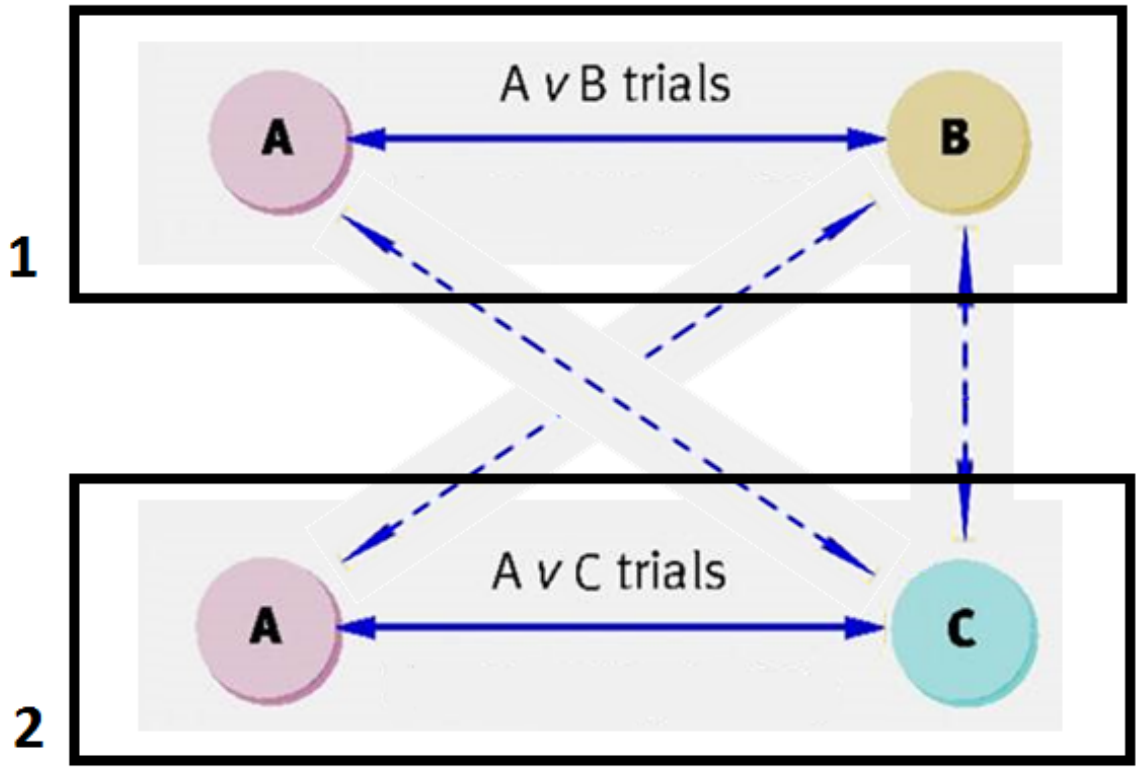

Figure 1.1 Schematic representation of network meta-analysis

In Box 1, two treatments for a given condition (A and B) have been compared in RCTs (A v B trials). The solid arrow between them represents a standard head-to-head, or pairwise MA, which summarises the effect estimate of treatment A compared to treatment B, as reported in those RCTs. Such methodology would be unable to simultaneously include a third available treatment C, (Box 2), which has been compared to treatment A in other RCTs (A v C trials), but would summarise this comparison separately (solid arrow). NMA on the other hand, allows inferences about the relationship between treatments B and C to be drawn (vertical dashed arrow), using the common comparator treatment A, even if there have been no B v C trials. This can also be expressed as:

$$C - B = (C - A) - (B - A)$$

NMA also uses the indirect evidence available in the network (diagonal dashed arrows) to increase the precision of the effect estimate for each of the included treatments, and to incorporate the totality of available RCT data.

The degree of connectedness of the various treatments through RCT head-to-head comparisons, or the 'geometry' of the network is a key consideration (Bafeta et al., 2014; Salanti et al., 2008a). For example, a 'star-shaped' network where all treatments have been compared to placebo only but not one another is too heavily reliant on indirect evidence which may introduce excess heterogeneity (Salanti et al., 2008b). The results of such NMAs should be interpreted with caution and should guide future trials by identifying missing evidence (Mills et al., 2013).

Another important principle in NMAs is the transitivity assumption (Efthimiou et al., 2016; Salanti, 2012). This is the premise that patients who were randomised to the different treatments in the included RCTs are similar, and that any patient can potentially receive any of the treatments compared in the network (Salanti et al., 2008a). Another way to consider this is whether each of the included network treatments could hypothetically make up one arm of a multi-group RCT (Salanti, 2012). Furthermore, each treatment within the network must be similar across all the studies that included it as a comparison (Chaimani et al., 2017). The network therefore becomes invalid if some of the included treatments are not clinically possible to administer to a subgroup of patients in the network, or if the administration of an included treatment was considerably different (Chaimani and Salanti, 2012; Donegan et al., 2010). This is an extension of the same principle in pairwise MA where the included RCTs compare identical treatment groups to which a sample patient population with the same clinical condition were randomised (Baker and Kramer, 2002).

As mentioned earlier, one of the strengths of NMA is the ability to draw on indirect evidence to increase the precision of the effect estimate and provide a comparison, even when no direct evidence is available. However, such indirect comparisons are not randomised and may suffer the biases of observational studies such as confounding (Jansen et al., 2008). They should therefore be used to supplement rather than supersede or replace direct evidence, although they can be more reliable in cases where direct evidence is only available from low quality RCTs (Donegan et al., 2010; Salanti et al., 2008a; Song et al., 2009). Testing for significant differences between the direct and indirect evidence for a given comparison within the network, termed inconsistency or incoherence, is an important step (Lumley, 2002; Riley et al., 2017; White et al., 2012). A statistical test for this is available within most packages (Chaimani et al., 2013), usually through the calculation of an inconsistency factor (Dias et al., 2010) or the difference between the direct

and indirect evidence within a 'closed' loop, or a loop formed by three (or four) treatments with direct and indirect comparisons between all of them (Efthimiou et al., 2016; Higgins et al., 2012). In addition, a manual comparison of the direct and indirect results should be performed (Chaimani et al., 2017) as lack of statistical evidence of inconsistency does not necessarily imply consistency (Bafeta et al., 2014). Statistical inconsistency should be investigated both qualitatively, by examining the contributing RCTs for heterogeneity, and quantitatively, using sensitivity analysis, before deciding on whether to include the indirect (and combined) evidence (Jansen et al., 2008; Salanti, 2012).

The included RCTs in any MA are not identical and clinical and methodological diversity inevitably leads to heterogeneity (Naylor, 1997). Testing for the degree of between-study statistical heterogeneity, or the differences between studies in terms of their treatment effect estimates is an integral component of pairwise MA through the calculation of the I^2 statistic (Higgins and Green, 2011). This describes the percentage of the between-study variability in effect estimates that is attributable to heterogeneity as opposed to chance or a sampling error. This is used along with a qualitative assessment to assess whether the heterogeneity in the included RCTs is significant or not (Mills et al., 2013). There is no direct equivalent to the I^2 statistic in NMA as there are multiple sources (direct and indirect) for each effect estimate (Caldwell et al., 2012), but calculation of predictive intervals (Bafeta et al., 2014) or the range within which any future RCT's effect estimate is likely to lie for that comparison (Chaimani et al., 2013) is a useful proxy (Salanti et al., 2014). Wide predictive intervals indicate that the contributing RCTs' results are heterogeneous, meaning that the NMA effect estimate for that comparison should be interpreted with caution (Chaudhry et al., 2015).

As discussed earlier, any statistical methodology is prone to misuse if not applied correctly and NMA is no exception (Salanti, 2012; Song et al., 2009). Guidelines groups recommend both expert statistical support and subject expertise to facilitate the preparation, conduct and reporting of NMA (Higgins and Green, 2011; Hutton et al., 2015; Salanti et al., 2014).

1.1.7 Applying NMA to surgical questions

Surgical practice, like all medical practice, is constantly changing. As new treatments, techniques and procedures become available, their potential benefits and harms need to be compared to

existing interventions (Potter et al., 2014). As discussed earlier, NMA synthesis has clear advantages over standard MA when more than two treatment options are being compared (Chaudhry et al., 2015). However, comparing drug treatments using NMA is more straightforward than comparing procedural interventions. This may explain why the uptake of NMA methodology has been quickest in medical disciplines where drug therapy is the mainstay, such as psychiatry (Cipriani et al., 2011; Cipriani et al., 2018a; Cipriani et al., 2018b; Cipriani et al., 2016; Davies et al., 2018; Miura et al., 2014) and cardiology (Palmer et al., 2015; Siontis et al., 2015; Wu et al., 2018). A recent review of all published NMAs found that 83% assessed pharmacological interventions (Bafeta et al., 2014).

A small number of NMAs addressing surgical interventions have been published, using relatively simple network constructs and variable statistical rigour (Bracale et al., 2012; Mazaki et al., 2015; Padwal et al., 2011; Simillis et al., 2015). Advanced NMA methods are well suited to answering many surgical questions where multiple options are available and have been compared in RCTs. Surgical RCTs are more methodologically heterogeneous than drug trials, so it is possible that this would lead to wide confidence intervals in a complex surgical NMA, and therefore uncertain effect estimates and rankings and clinically less meaningful conclusions.

The first part of this thesis utilises advanced NMA to address two practical surgical questions; carbohydrate loading prior to elective surgery, and anti-reflux surgery. These examples demonstrate different applications of NMA methodology, and in both examples the results provide new information and conclusions that were not evident from existing published MAs.

1.2 Bias in clinical trials

Although RCTs are the gold standard method for assessing the benefits and harms of healthcare interventions, their results are only valid if they are well designed and conducted (Sinha et al., 2009). RCT validity has two main components, referred to as external validity (whether the RCT question is appropriate and clinically meaningful) and internal validity (whether the RCT answers the question in a manner that is free from bias) (Juni et al., 2001). Factors that affect external validity vary depending on the subject matter and will not be discussed further here.

Bias is defined as systematic distortion of a statistical result (Fowler and Fowler, 2011). This can lead to either an under- or over-estimation of the true treatment effect in an RCT (Wood et al., 2008), leading to false positive or false negative results, particularly with respect to subjective outcomes (Hrobjartsson et al., 2014). Such bias often arises unintentionally from subconscious tendencies (Day and Altman, 2000) including the so-called placebo effect.

1.2.1 The placebo effect

The word placebo is defined as a medicine or procedure prescribed for psychological, rather than physiological effect (Fowler and Fowler, 2011). Meaning "I shall please" in Latin, the term was introduced into medicine in the late 18th century to mean a treatment that is given to please, placate or console rather than benefit the patient (Bernstein and Brown, 2017; de Craen et al., 1999; Sonawalla and Rosenbaum, 2002). The placebo effect relates to our psychological predisposition to hope and positive expectation, and is well known to influence our judgement of the efficacy of a treatment (Beecher, 1955; Feys et al., 2014). Optimism bias, a term borrowed by Sir Iain Chalmers from the psychology literature, refers to the tendency for patients to assume that novel treatments are an advance on currently available ones (Chalmers, 1997; Chalmers and Matthews, 2006).

Observer bias, also known as ascertainment or detection bias (Hrobjartsson et al., 2012), can be thought of as the equivalent phenomenon affecting the treatment administrator (or assessor), resulting from the interaction between the observer's predispositions and the subjectivity of the outcome being assessed (Hrobjartsson et al., 2014). This is particularly influential when investigators have strong convictions regarding the evaluated treatment, leading to intervention preoccupation (overrating the intervention group) (Hrobjartsson et al., 2012) or compliant responses from patients (Beecher, 1955; Spanos et al., 1992).

The 'bias blind spot' is a term coined by Emily Pronin, a social psychologist at Princeton University, to describe the natural tendency of recognising the impact of biases on the judgement of others while failing to see the impact of biases on one's own judgement (Pronin et al., 2002). One of her group's findings in a study of 600 US residents was that more than 85% believed they were less biased than the average American, and only one participant thought they were more biased than average.

The placebo effect and bias blind spot are just two examples of a range of factors that can introduce bias in an RCT, significantly altering the results. This in turn can affect the conclusions of subsequent synthesis (Goodman and Dickersin, 2011; Moher et al., 1998) and lead to erroneous recommendations for clinical practice (Detsky et al., 1992). Classifying and controlling for potential sources of bias is therefore critical to the validity of healthcare intervention RCTs.

1.2.2 Common sources of bias

The Cochrane Collaboration's tool for assessing the risk of bias in RCTs (Higgins et al., 2011) employs a useful classification into selection, performance, detection, attrition and reporting bias, with definitions for each (Higgins and Green, 2011). A brief outline of this follows, along with strategies to effectively minimise the influence of these biases as recommended by the Cochrane Collaboration and guidelines groups (Higgins and Green, 2011; Schulz et al., 2010).

Selection bias is used to describe systematic differences between the baseline characteristics of study groups. It is avoided by effective randomisation, which has two essential components, namely the generation of an allocation (or randomisation) sequence that is based on chance and strict implementation of that random sequence by concealment, meaning that it is impossible to know which group the next trial participant will be allocated to (Odgaard-Jensen et al., 2011).

Systematic differences between the groups in the provided care or in exposure to factors other than the intervention of interest is referred to as performance bias. The risk of such bias is minimised by blinding (Savovic et al., 2012), or ensuring that study participants do not know which group they were allocated to. Blinding of study investigators additionally ensures that all participants, regardless of the group they were allocated to, receive identical treatment apart from the trial interventions. Outcome differences between the groups are therefore more likely to reflect differences in intervention effect (Hall, 2010). This is particularly important in instances where there are prevalent preconceptions about a particular therapy.

Detection bias refers to systematic variation between the groups in the way outcomes are assessed and recorded, and is particularly problematic when evaluating subjective outcomes. Paradoxically, some conscientious assessors may overcompensate for an expected subconscious bias in favour of

the intervention by consciously favouring the control (Hrobjartsson et al., 2013). Detection bias is countered by blinding the outcome assessors (Wood et al., 2008). Other strategies such as the use of correlation coefficients to assess inter-observer agreement are not effective (Hrobjartsson et al., 2013).

Systematic disparity between the groups in study withdrawals and exclusions is referred to as attrition bias, and leads to non-random missing outcome data. This can be because data of some trial participants have been intentionally excluded from the analyses or are not available to the investigators (Wood et al., 2008). Performing an intention-to-treat (or as per randomisation) instead of an as-treated (or per protocol) analysis can minimise this risk of bias (Juni et al., 2001).

Finally, reporting bias (or selective reporting bias) refers to systematic differences between the reported and unreported findings of a study (Chalmers, 1990; Higgins and Green, 2011; McGauran et al., 2010). This usually manifests as preferential reporting of results with statistically significant differences. There are other potential sources of reporting bias such as the use of different time-points, outcome assessment instruments or analyses to show a statistically significant difference (Chalmers et al., 2013). The risk of reporting bias is minimised by determining *a priori* how the data will be analysed and reported, publishing a trial protocol including a detailed statistical analysis plan and publishing all the results (Schulz et al., 2010).

Other biases and factors may affect the results of RCTs. These include contamination (where participants of a drug versus placebo trial decide to mix and evenly distribute the trial drugs so each participant has an equal chance of receiving the active treatment) and co-intervention (where study controls are provided non-study interventions by well-meaning carers) (Dechartres et al., 2013; Sackett, 2007; Shun-Shin and Francis, 2013). However, the classification described above covers the common sources of bias. The effect of these biases on the results of RCTs can be examined in methodological studies using meta-epidemiology techniques.

1.2.3 Meta-epidemiology

A meta-epidemiological study analyses MAs with respect to a particular methodological or other study-level characteristic in the included RCTs (Sterne et al., 2002). In brief, the difference in the pooled effect estimate (such as the odds ratio or mean difference) between studies that contain that

characteristic (such as blinding) and those that do not is calculated within each meta-analysis. These differences (or ratios) are then combined across the meta-analyses into what is also called a meta-meta-analysis (Higgins and Green, 2011). The result is a quantitative estimate of the effect of that study-level characteristic on the RCTs' results.

Recent meta-epidemiological studies have provided empiric evidence that the potential sources of bias discussed earlier significantly influence the results of RCTs by exaggerating the effect estimate of the studied treatment (Savovic et al., 2012; Schulz et al., 1995; Wood et al., 2008). Selection, performance and detection bias have been found to be particularly influential, with a combined exaggerated treatment effect of up to 37% (Moher et al., 1998; Wood et al., 2008). A recent editorial clearly demonstrated this cumulative bias effect using trials assessing renal artery denervation for the treatment of hypertension as an example (Shun-Shin et al., 2014).

The methodological studies performed to date have pooled data from trials across several medical disciplines with RCTs of pharmacological interventions constituting the vast majority. Surgical RCTs have important differences to drug trials (Barkun et al., 2009; Love, 1975; Solomon and McLeod, 1995) and these differences influence susceptibility to various forms of bias (Stirrat et al., 1992).

1.2.4 Considerations in surgical trials

The impossibility of blinding the operating surgeon, and the difficulties in blinding patients and carers to surgical procedures, are well recognised (Boutron et al., 2004; Hill et al., 2002; Schulz and Grimes, 2002). There is ample evidence that the placebo effect of procedures is even greater than for drugs (Kaptchuk et al., 2000; McRae et al., 2004). Some authors have argued that blinding in surgical trials is not possible, and should not be considered (Patel et al., 2013; Pham et al., 2009; Vinuela et al., 2012). A review of orthopaedic trauma trials reported that outcome assessment had not been blinded in 90% of trials (Karanicolas et al., 2008), even though that was possible (Bingener et al., 2015; McCulloch et al., 2002). Such widespread non-blinding is likely to influence the results and interpretation of many surgical RCTs (Penninga et al., 2014).

Surgical RCTs are affected by surgeon and patient preference in procedure selection and patient eligibility (Jack et al., 1990; Lassen et al., 2005), with greater optimism bias. This may persist

even after blinded evaluation shows no benefit in the novel procedure (Freed et al., 2001; Wartolowska et al., 2014). Procedures such as laparoscopic cholecystectomy spread rapidly due to surgeon and patient enthusiasm before RCT evaluation (Cuschieri, 1989; Cuschieri et al., 1990; Russell, 1995). Optimism bias can also lead to cross-over of enrolled patients between treatment groups, which may significantly influence the results in an intention-to-treat (or as randomised) analysis (Cunningham, 2011).

Expert opinion can sometimes suggest that surgical RCTs are impractical or inappropriate (Kenny et al., 1997), which may or may not be justified (Gattellari et al., 2001; McCulloch et al., 2002; Meakins, 2006). The influence of selection bias may therefore increase in surgical trials if appropriate generation of the randomisation sequence and allocation concealment is not employed.

Multiple other factors contribute to the added complexity of surgical RCTs compared to drug trials, such as the difficulty of standardising interventions and procedures (Neugebauer et al., 1991; Sinha et al., 2009; Solomon and McLeod, 1995) and the timing of an RCT for a novel intervention with respect to the learning curve (Ergina et al., 2009; McCulloch et al., 2002).

One of the conclusions of the Balliol Colloquia, a series of meetings between 2007 and 2009 at the eponymous College in Oxford, held to discuss the advancement of surgical research (Waxman, 2016), was that none of these challenges were beyond the design of a clinical trial (Lancet, 2009). Indeed, some of the earliest high quality RCTs were designed and conducted by surgeons (Cobb et al., 1959; Dimond et al., 1960; Livingston, 1953), with John Goligher's RCT on duodenal ulcer surgery being an excellent early example that included random sequence generation, allocation concealment, blinded outcome assessment and >99% follow-up (Goligher et al., 1964). Surgical RCTs can therefore be held to the same high standards as other trials (Horton, 1996; Stirrat et al., 1992).

The question of whether blinding and other sources of bias significantly influence the results of surgical RCTs is important for two reasons. Firstly, there are implications for the interpretation of published surgical RCTs that form the basis of current evidence-based surgical practice. Secondly, this information will help guide future surgical RCT design. Although difficult to incorporate and therefore seldom attempted, blinding should be considered in the design of future

surgical trials if shown to have a significant impact on outcome measures. The second part of this thesis reports on a meta-epidemiological study that specifically examined this question.

1.3 Aims

The aims of this thesis are:

1. To apply network meta-analysis techniques to specific surgical questions.
2. To determine the effect of blinding, and other bias-minimisation strategies, on the results of surgical randomised clinical trials

Chapter Two uses NMA methods to investigate the efficacy of preoperative carbohydrate loading for patients undergoing elective surgery. A number of published pairwise meta-analyses reported conflicting conclusions, as they were unable to account for the different doses, and control treatments, used in the RCTs.

NMA methodology is used in Chapter Three to determine which anti-reflux operation provides the best balance of benefit and risk for the treatment of gastro-oesophageal reflux disease (GORD). This has remained an unresolved question despite dozens of RCTs and numerous pairwise MAs.

Chapter Four uses meta-epidemiological methods to quantify the effect of lack of blinding and other methodological deficiencies that pose a risk of bias, on surgical RCT results. It draws on individual trial level data from over 300 RCTs of laparoscopic versus open surgical procedures.

CHAPTER TWO

Systematic review and network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery

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My contribution to this chapter

This project was conceived jointly by myself and my supervisors (JLM, GPH and MDS). It builds on earlier work published by them and other co-authors (Smith et al., 2014). I updated the systematic search, selected and extracted data from additional eligible trials (with co-author duplication) and performed all of the analysis with guidance from GPH and MDS. All drafts and the final manuscript of the resulting publication were written by myself, with revisions in conjunction with my supervisors and journal reviewers. This chapter is adapted from the published paper (Amer et al., 2017).

2.1 Chapter summary

Recent MAs have summarised the results of RCTs investigating the effects of preoperative carbohydrate (CHO) administration on clinically relevant postoperative outcomes in adult patients undergoing elective surgery. However, these MAs could not account for the different doses of CHO administered and the different controls used. NMA allows for robust synthesis of all available evidence in these situations. Article databases were systematically searched for RCTs comparing preoperative carbohydrate administration with water, a placebo drink or fasting. A four

treatment NMA was performed comparing two CHO dose groups (low: 10–44g; high: >45g) with two control groups (fasting; water or placebo). Primary outcomes were length of hospital stay and the postoperative complication rate. Secondary outcomes included postoperative insulin resistance, vomiting and fatigue. Forty three trials involving 3110 participants were included. Compared to fasting, preoperative low dose and high dose CHO administration decreased postoperative length of stay by 0.4 days (95% confidence interval (CI) 0.03 – 0.7) and 0.2 days (95% CI 0.04 – 0.4) respectively. There was no significant decrease in length of stay compared to water or placebo. There was no significant difference in the postoperative complication rate or in most of the secondary outcomes between the CHO and control groups. These results show that preoperative CHO administration is safe, but does not provide a clinically relevant benefit over water or a flavoured drink.

2.2 Introduction

Enhanced recovery after surgery (ERAS), or fast-track recovery, is a set of perioperative principles and strategies brought together in an integrated pathway to optimise patients' operative journeys and minimise morbidity. ERAS is now in widespread use across many surgical disciplines internationally, as it has been shown to reduce complications, facilitate recovery and hasten discharge (Gouvas et al., 2009).

However, the evidence supporting the use of some individual components of ERAS is variable, meaning their routine inclusion in ERAS remains debatable (Lubowski, 2014). An example of this is the preoperative administration of a CHO load, usually as an oral solution, promoted as a counter to postoperative hyperglycaemia (Ljungqvist et al., 2002).

Surgery, as a form of stress, is known to induce peripheral insulin resistance which can lead to hyperglycaemia, which in turn may lead to postoperative complications and prolonged recovery (Nygren, 2006). Studies have shown that a preoperative CHO load large enough to stimulate a prompt insulin response decreases postoperative insulin resistance by around 50% (Ljungqvist et al., 2002). Over 30 RCTs have investigated whether this effect results in improved postoperative outcomes. These have been summarised in several recent MAs (Awad et al., 2013; Li et al., 2012; Smith et al., 2014).

However, these MAs arrived at variable conclusions. This variability is partly due to different inclusion and exclusion criteria, meaning different RCTs were included in each MA. More importantly however, a standard pairwise MA cannot account for the different CHO doses and different controls used in the included RCTs. As a result, these MAs either combined different control groups (such as fasting, water and placebo) into one treatment arm (Awad et al., 2013; Smith et al., 2014) or performed several different head-to-head MAs (Li et al., 2012; Smith et al., 2014), thereby limiting their interpretability. Thus, there remains a need for an inclusive, methodologically sound analysis of all the available evidence to resolve ongoing uncertainty around the true clinical benefits of CHO loading (Zargar-Shoshtari and Hill, 2008).

NMA offers a validated method of synthesis in instances such as this, as detailed in Chapter 1. This chapter reports the results of a systematic review and NMA to determine the effects of preoperative CHO administration on clinically relevant postoperative outcomes in adult patients undergoing elective surgery.

2.3 Methods

2.3.1 Search strategy and selection criteria

A systematic review of RCTs of preoperative CHO administration for elective surgical patients was performed using the same process and outcomes described in the Cochrane review on the same topic (Smith et al., 2014). In brief, article databases and trial registries were searched to June 2016 using a structured sensitivity maximising search strategy (Appendix B1) and no language restrictions. All citations were in English, as translated by the databases. Abstracts and full texts in French, German and Japanese were able to be translated by the data extractors. Studies in other languages were translated using Google translate (Jackson et al., 2019). Two authors independently screened all titles and abstracts for eligibility, and trial authors were contacted when further information was required to decide on eligibility.

All randomised and quasi-randomised trials comparing the preoperative administration of at least 10g CHO (either orally or intravenously) within 4 hours of surgery start time with fasting, water or placebo, to adults undergoing any type of elective surgical procedure were included. Studies

that co-administered other substances (such as glutamine) were included as long as the dose of CHO was greater than 10g. Studies that did not administer CHO within four hours prior to surgery and studies that included patients undergoing emergency surgery (defined as within 24 hours of first physician contact) were excluded.

2.3.2 Outcome measures

All trials that reported any of the following outcomes were included.

Primary outcomes:

1. Length of postoperative stay (in days).
2. Postoperative complication rate (as defined by trial authors).

Secondary outcomes:

1. Aspiration pneumonitis rate (defined as observed regurgitation or vomiting in association with abnormal chest imaging).
2. Vomiting within the first 24 hours postoperatively (measured as an incidence count).
3. Insulin resistance (measured by the Homeostatic model assessment of insulin resistance (HOMA-IR) method).
4. Insulin sensitivity (measured by the hyperinsulinaemic-euglycaemic clamp method).
5. Nausea at 24 hours postoperatively (measured on ordinal, visual analogue or composite scales).
6. Postoperative general well-being (measured on ordinal, visual analogue or composite scales).
7. Postoperative fatigue (measured on ordinal, visual analogue or composite scales).
8. Return of intestinal function (number of postoperative days to first passage of flatus, and first passage of bowel motion).

2.3.3 Data extraction and quality assessment

For studies that were also included in the Cochrane review (Smith et al., 2014), data already extracted were used. For the additional studies included in this review, the same structured paper form used in the Cochrane review was employed to collect extracted data (Appendix B2). Extracted data included study characteristics, patient characteristics, intervention details and outcome measures. Study authors were contacted to request missing data necessary for NMA.

Missing standard deviations were calculated from standard errors or confidence intervals (Higgins and Green, 2011), or from ranges or interquartile ranges (Hozo et al., 2005). When standard deviations could not be calculated, and attempts to contact the study authors were exhausted, they were imputed using the median of reported standard deviations from other similar trials.

The methodological quality of all included trials was assessed using the Cochrane Risk of Bias tool (Higgins et al., 2011) across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential sources of bias (such as baseline imbalances or differential diagnostic activity). Each domain was assessed as high risk, low risk or unclear risk.

2.3.4 Statistical analysis

A random-effects NMA was performed using the suite of Stata (StataIC 13, StataCorp LP., College Station, Texas) routines developed specifically for this purpose (Chaimani et al., 2013; Chaimani and Salanti, 2015; White, 2015). The main analysis comprised four treatment groups (nodes): low dose CHO (10g – 44g), high dose CHO (≥45g), water/placebo and fasting. Fasting was allocated as the reference treatment in the network. Comparisons between the water/placebo group and the fasting group are not reported as this review does not include all RCTs that compared preoperative fasting with water only. CHO arms of multiple-group RCTs where those arms received the same amount of carbohydrate (with or without additives such as glutamine) were combined. A network map was produced to provide a visual summary of the network of evidence available.

The results for continuous data were summarised as a mean difference (MD) or standardised mean difference (SMD) as appropriate, with 95% confidence intervals (CI). An SMD was used if studies assessing the same outcome used different measures or the results for that outcome were substantially different due to study population differences. Categorical data were summarised as an odds ratio with 95% CI. Where an SMD was appropriate, the original result in standard deviations (SD) is reported as well as the back-transformed approximations to the initial unit (Higgins and Green, 2011).

For primary outcomes with statistically significant differences between the groups, the probability of each treatment group ranking as the best, second, third or worst treatment in the network was

calculated and presented as a rankogram if one treatment was clearly superior (>90% probability of ranking best) (Dias et al., 2012).

A meta-regression analysis for outcomes with statistically significant differences between the groups was also performed to further evaluate any relationship with CHO dose. The network meta command (Chaimani et al., 2013) was run, and the resulting effect estimate and standard error for each study were used to run metareg (Harbord and Higgins, 2008). Both the R^2 value and 'bubble plot' (regression line of best fit) were inspected to determine whether a dose–response relationship existed. Three-arm trials (where two different carbohydrate doses were used) were dealt with by using the two effect estimates derived from them as two separate entries into metareg. A sensitivity analysis was performed for this by assuming they were two different studies then serially excluding each entry.

Cumulative pairwise MA for the outcome of length of postoperative stay was also performed. This was undertaken with R (Version 3.3.1, R Foundation for Statistical Computing, Vienna) using the meta package (Schwarzer, 2016). High-dose carbohydrate was compared with placebo, water or fasting, with studies being sequentially added by date of publication.

Subgroup analyses by type of surgery for outcomes where there were sufficient data to allow for this were performed. Major surgery was defined as all procedures with a reported mean length of postoperative stay of two or more days, and minor surgery as all procedures with a reported mean length of postoperative stay of less than two days.

Several sensitivity analyses were performed. First, the influence of imputed versus reported data was assessed by excluding studies where data were imputed. Second, the transitivity assumption was tested by splitting the 'water or placebo' node within the network. Third, blinded trials were analysed as a separate node within the network to assess the influence of un-blinded studies.

Between-study heterogeneity was assessed by calculating predictive intervals, or the interval within which the treatment effect estimate of a future study is expected to lie (Chaimani et al., 2013). Inconsistencies between direct and indirect evidence in the network (loop-specific

heterogeneity) were also tested for by calculating the difference between the two (the inconsistency factor) in each closed loop (Dias et al., 2010).

To investigate publication bias a comparison-adjusted funnel plot was visually inspected, which accounted for the fact that the included studies estimated treatment effects for different comparisons (Chaimani et al., 2013).

2.4 Results

2.4.1 Search results and study characteristics

The database search and study selection process is summarised in Figure 2.1. Forty-three RCTs fulfilled the inclusion criteria, involving 3110 patients (Table 2.1).

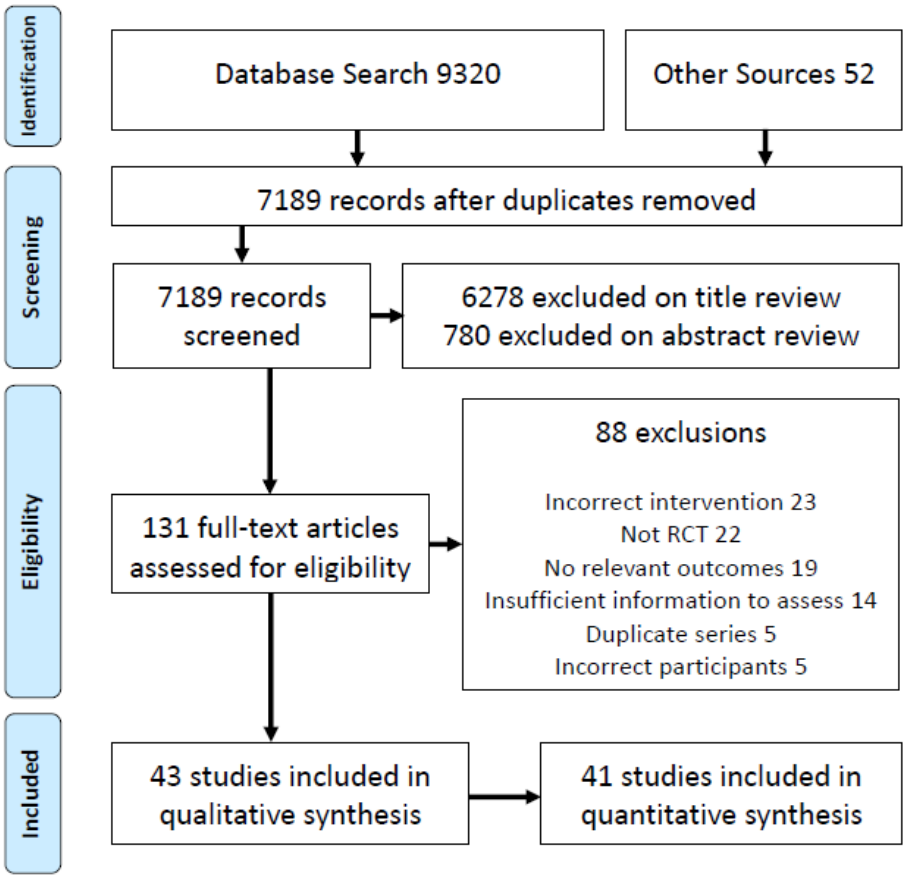

Figure 2.1 Systematic search and study selection flowchart

Table 2.1 Details of included studies

Reference	Country	Type of elective surgery	CHO dose and route*†	Control†	No. of patients	ASA grade
(An et al., 2008)	China	Colonic cancer resection	50g, oral	Fasting	51	NR
(Aronsson et al., 2009)	Sweden	Hip replacement	25g, oral	Flavoured water	28	NR
(Asakura et al., 2015)	Japan	Body surface surgery‡	45g, oral§	Fasting	91	I–II
(Bisgaard et al., 2004)	Denmark	Laparoscopic cholecystectomy	50g, oral	Placebo¶	86	I–II
(Braga et al., 2012)	Italy	Pancreaticoduodenectomy	50g, oral	Low energy drink#	36	NR
(Breuer et al., 2006)	Germany	CABG or valve replacement	50g, oral	Placebo¶; fasting	160	III–IV
(Canbay et al., 2014)	Turkey	Open radical prostatectomy	50g, oral	Fasting	50	I–II
(Chen et al., 2014)	China	Open gastrectomy for cancer	50g, oral	Water; fasting	36	NR
(Chen et al., 2015)	China	Open gastrectomy for cancer	50g, oral	Fasting	35	NR
(Dock-Nascimento et al., 2012)	Brazil	Laparoscopic cholecystectomy	25g, oral	Water; fasting	48	I–II
(Faria et al., 2009)	Brazil	Laparoscopic cholecystectomy	25g, oral	Fasting	21	I–II
(Feguri et al., 2012)	Brazil	CABG	25g, oral	Water	40	NR
(Harsten et al., 2012)	Sweden	Hip replacement	50g, oral	Placebo¶	60	I–III
(Hausel et al., 2005)	Sweden	Laparoscopic cholecystectomy	50g, oral	Placebo¶; fasting	172	I–II
(Henriksen et al., 2003)	Denmark	Bowel resection	50g, oral	Fasting	48	NR
(Itou et al., 2012)	Japan	Mixed**	12.5g, oral	Fasting	274	I–II
(Jarvela et al., 2008)	Finland	CABG	50g, oral	Fasting	101	NR

Table 2.1 continued

Reference	Country	Type of elective surgery	CHO dose and route*†	Control†	No. of patients	ASA grade
(Karlsson et al., 2016)	Sweden	Laparoscopic Roux-en-Y gastric bypass	50g, oral††	Water	51	NR
(Kaska et al., 2010)	Czechia	Colorectal surgery	50g, oral; 25g, IV	Fasting	221	I–II
(Lauwick et al., 2009)	Belgium	Thyroidectomy	50g, oral	Water	200	I–II
(Lidder et al., 2013)	UK	Colorectal surgery	50g, oral	Placebo‡	120	NR
(Ljunggren and Hahn, 2012)	Sweden	Hip replacement	50g, oral	Water; fasting	57	I–III
(Ljunggren et al., 2014)	Sweden	Hip replacement	50g, oral	Flavoured water	22	I–III
(Ljungqvist et al., 1994)	Sweden	Open cholecystectomy	250g, IV‡‡	Fasting	12	NR
(Mathur et al., 2010)	New Zealand	Colorectal or liver resection	50g, oral	Placebo¶	142	I–III
(Meisner et al., 2008)	Germany	Laparoscopic gynaecological surgery	30g, oral§§	Fasting	42	I–II
(Noblett et al., 2006)	UK	Colorectal surgery	47.5g, oral	Water; fasting	35	Median II
(Ozdemir et al., 2011)	Turkey	Hysterectomy¶¶ or inguinal hernia repair##	50g, oral	Water; fasting	90	I–II
(Perrone et al., 2011)	Brazil	Cholecystectomy*** or inguinal hernia repair	54g, oral	Water	17	I–II

Table 2.1 continued

Reference	Country	Type of elective surgery	CHO dose and route*†	Control†	No. of patients	ASA grade
(Pexe-Machado et al., 2013)	Brazil	Laparotomy for gastrointestinal malignancy†††	67g, oral	Fasting	22	I–III
(Raksakietisak et al., 2014)	Thailand	Unilateral total knee joint replacement	40g, oral	Fasting	98	I–III
(Rapp-Kesek et al., 2007)	Sweden	CABG	50g, oral	Fasting	18	NR
(Sada et al., 2014)	Kosovo	Colorectal resection or open cholecystectomy‡‡‡	50g, oral	Placebo¶; fasting	138	I–II
(Singh et al., 2015)	India	Laparoscopic cholecystectomy	25g, oral	Flavoured water; fasting	120	NR
(Soop et al., 2001)	Sweden	Hip replacement	50g, oral	Placebo¶	15	NR
(Soop et al., 2004)	Sweden	Hip replacement	50g, oral	Placebo¶	14	I–II
(Tran et al., 2013)	Canada	CABG or spinal surgery with fusion	50g, oral	Fasting	38	NR
(Wang et al., 2010)	China	Open colorectal cancer surgery	50g, oral	Placebo¶; fasting	48	NR
(Yang et al., 2012)	China	Open radical distal gastrectomy	50g, oral	Sweetened water§§§	48	NR
(Yildiz et al., 2013)	Turkey	Laparoscopic cholecystectomy	50g, oral	Fasting	60	I–II
(Yilmaz et al., 2013)	Turkey	Laparoscopic cholecystectomy	50g, oral	Fasting	40	I–II

Table 2.1 continued

Reference	Country	Type of elective surgery	CHO dose and route*†	Control†	No. of patients	ASA grade
(Yuill et al., 2005)	UK	Open major abdominal surgery¶¶¶	50.4g, oral	Placebo¶	65	NR
(Zelic et al., 2012)	Croatia	Colorectal cancer surgery	50g, oral	Fasting	40	I–II

*CHO dose administered within 4h of surgery start time, calculated using reported volumes and concentrations. †Multiple groups separated by semicolon. ‡Across multiple disciplines, as reported by the study authors; most patients underwent transperineal prostate brachytherapy. §The study included a treatment group of patients who were given a 2.5% oral CHO solution, to be consumed from the night before to 2h before surgery; this group was excluded as the amount of CHO received within 4h of surgery start time was less than 10g. ¶A specially formulated oral solution, reported to be indistinguishable from the CHO solution. #Oral drink containing orange juice, starch, sodium, saccharine and colours. **Patients underwent otorhinolaryngeal, orthopaedic, plastic, gynaecological, breast, thyroid or thoracic surgery. ††The study included a treatment group of patients who were given a protein-rich solution containing 2.8g CHO, 2h before surgery; this group was excluded as the amount of CHO was less than 10g. ‡‡Calculated approximation; patients received an IV glucose infusion at 5mg/kg/min from within 1h after the last meal on the night before surgery (approximately 06.00 hours), to within 30–60 min before induction of anaesthesia the following morning (between 08.30 and 12.30 hours). §§Patients were allowed an unlimited intake of an oral CHO drink; the reported average intake was 250 ml (30 g). ¶¶Abdominal approach. ##Patients were randomly allocated to a treatment arm within each of the two operative categories (major, hysterectomy; minor, inguinal hernia), and the authors reported the results for each category separately. ***Open or laparoscopic. †††Procedures included subtotal gastrectomy, hemicolectomy and anterior resection. ‡‡‡Patients were randomly allocated to a treatment arm within each of the two operative categories (colorectal resection and open cholecystectomy), and the authors reported the results for each category separately. §§§CHO-free. ¶¶¶Procedures included liver resection, pancreatic resection and gastrectomy. ASA, American Society of Anesthesiologists; CHO, carbohydrate; IV, intravenous; NR, not reported; CABG, coronary artery bypass grafting.

One trial (Aronsson et al., 2009) could not be included in the NMA as the only relevant reported outcome was the aspiration pneumonitis rate, which was zero across all groups in all RCTs. Another trial (Singh et al., 2015) reported nausea as a mean incidence rate which could not be included in the NMA but is included in the qualitative synthesis.

Patients in the included RCTs underwent a wide variety of open and laparoscopic surgical procedures for benign and malignant pathology including colorectal and upper gastrointestinal surgery, endocrine surgery, orthopaedic surgery, cardiothoracic surgery and gynaecological surgery. The majority of RCTs were conducted in Europe and involved the administration of high dose CHO preoperatively (mostly 45 – 55g). Two studies administered CHO intravenously (Kaska et al., 2010; Ljungqvist et al., 1994) and only one study directly compared low and high dose CHO (Kaska et al., 2010).

The risk of bias assessment of the included trials is presented in Figures 2.2 and 2.3. Of the 43 included trials, only six were judged as adequately blinded with low risk of performance or detection bias (Bisgaard et al., 2004; Lidder et al., 2013; Mathur et al., 2010; Soop et al., 2001; Soop et al., 2004; Yuill et al., 2005). There was evidence of selection bias in the majority of the included studies. Only two trials (Lidder et al., 2013; Mathur et al., 2010) were judged as low risk of bias across all domains.

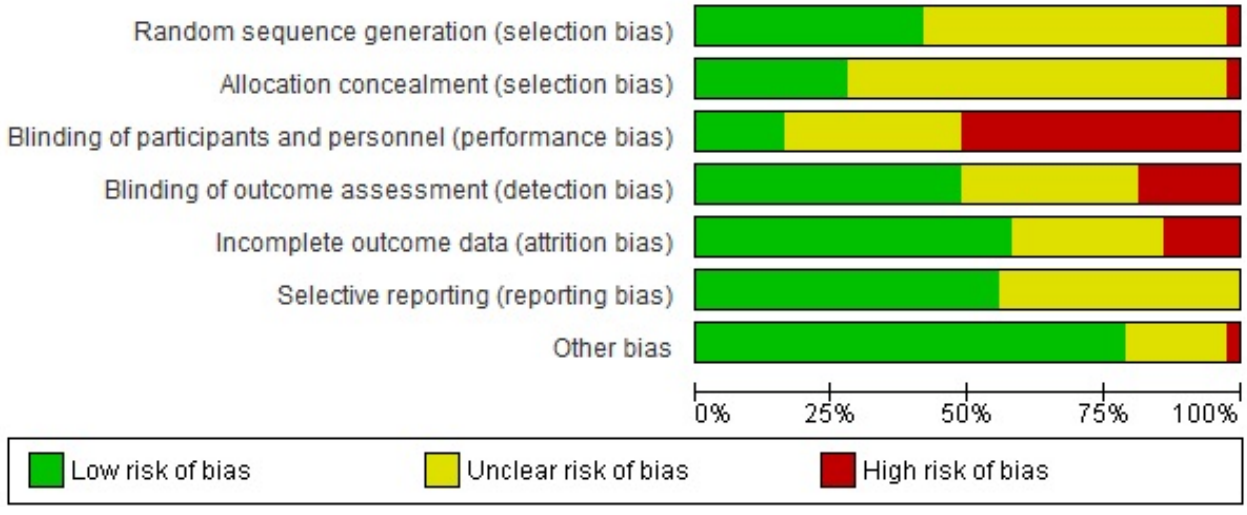

Figure 2.2 Risk of bias assessment summary figure

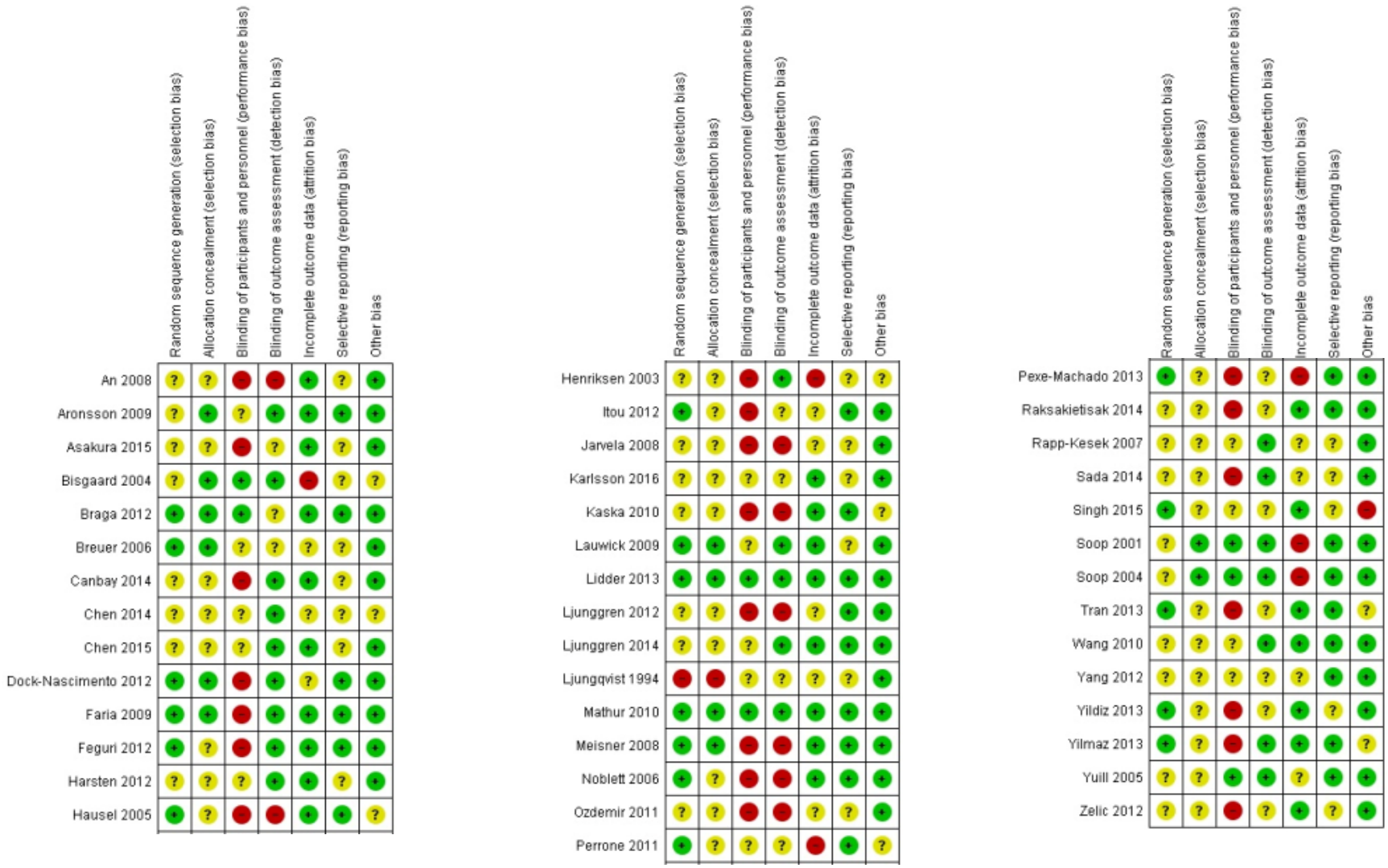

Figure 2.3 Risk of bias assessment by individual study

+ denotes low risk; ? denotes unclear risk; − denotes high risk of bias, for each given domain, as judged by the authors.

2.4.2 Length of postoperative stay

Length of postoperative stay was the most commonly reported outcome and was therefore used for the sensitivity analyses and funnel plot. Figure 2.4 summarises the network of direct evidence available for this outcome. This was reported by twenty five studies involving 1890 participants (An et al., 2008; Asakura et al., 2015; Braga et al., 2012; Breuer et al., 2006; Canbay et al., 2014; Dock-Nascimento et al., 2012; Feguri et al., 2012; Harsten et al., 2012; Hausel et al., 2005; Kaska et al., 2010; Lidder et al., 2013; Ljunggren and Hahn, 2012; Mathur et al., 2010; Noblett et al., 2006; Ozdemir et al., 2011; Perrone et al., 2011; Pexe-Machado et al., 2013; Raksakietisak et al., 2014; Sada et al., 2014; Soop et al., 2001; Soop et al., 2004; Tran et al., 2013; Yang et al., 2012; Yildiz et al., 2013; Yuill et al., 2005).

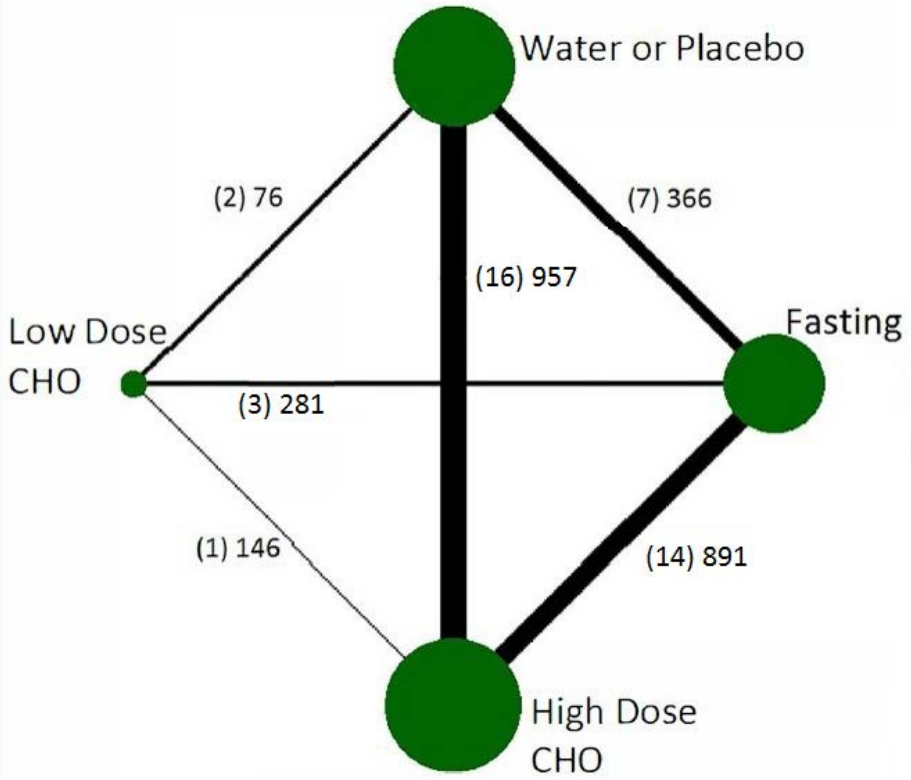

Figure 2.4 Network map for evidence for length of postoperative stay

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 pair of treatments. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

CHO = Carbohydrate.

Mean length of postoperative stay in the included studies ranged from one day to seventeen. NMA results are presented in Figure 2.5 and Table 2.2. Compared to fasting, patients administered CHO preoperatively were discharged earlier (high dose CHO 0.2 SD earlier [SMD, 95% CI 0.04 – 0.4], low dose CHO 0.4 SD earlier [SMD, 95% CI 0.03 – 0.7]). On back-transformation into days, high dose CHO administration decreased length of stay for patients undergoing major surgery (mean length of stay >2 days) by 0.7 days (95% CI 0.1 – 1.4), and for patients undergoing minor surgery (mean length of stay <2 days) by 0.07 days (95% CI 0.01 – 0.1). When compared to water or placebo, no significant benefit was shown for either low or high dose CHO with respect to time to hospital discharge. No statistically significant difference was found between the two CHO groups in the network. None of the treatments was clearly superior on calculation of ranking probabilities for this outcome.

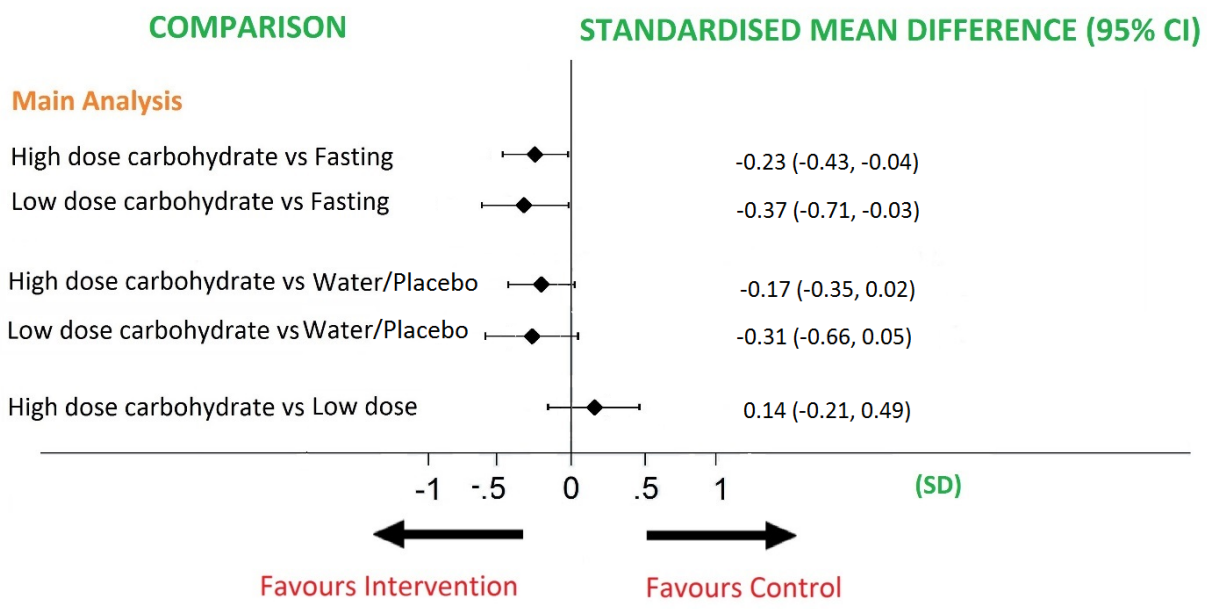

Figure 2.5 Composite forest plot of comparisons for length of postoperative stay

Boxes and horizontal lines represent the standardised mean difference and 95% confidence intervals for each comparison, respectively.

SD = Standard deviation. SMD = Standardised mean difference.

Table 2.2 Network meta-analysis results

	vs Fasting	vs Water/Placebo	vs Low dose CHO
Length of postoperative stay			
High dose CHO*	-0.2 SD (-0.4, -0.04) †	-0.2 SD (-0.4, 0.02)	0.1 SD (-0.2, 0.5)
Low dose CHO*	-0.4 SD (-0.7, -0.03) †	-0.3 SD (-0.7, 0.05)	
Back-Transformation‡			
Major Surgery§			
High dose CHO	-0.7 days (-1.4, -0.1) †	-0.7 days (-1.4, 0.07)	0.3 days (-0.7, 1.7)
Low dose CHO	-1.4 days (-2.4, -0.1) †	-1.0 days (-2.4, 0.2)	
Minor Surgery¶			
High dose CHO	-0.07 days (-0.1, -0.01) †	-0.07 days (-0.1, 0.01)	0.04 days (-0.07, 0.2)
Low dose CHO	-0.1 days (-0.2, -0.01) †	-0.1 days (-0.2, 0.02)	
Subgroup Analysis#			
Major Abdominal Surgery			
High dose CHO	-1.7 days (-3.2, -0.1) †	-1.4 days (-2.7, -0.1) †	0.2 days (-3.1, 3.6)
Low dose CHO	-1.9 days (-5.2, 1.5)	-1.6 days (-5.1, 1.9)	
Minor Abdominal Surgery			
High dose CHO	-0.09 days (-0.4, 0.2)	0.0 days (-0.05, 0.05)	-0.02 days (-0.4, 0.4)
Low dose CHO	-0.07 days (-0.5, 0.4)	0.02 days (-0.4, 0.4)	
Orthopaedic Surgery			
High dose CHO	-0.7 days (-2.3, 1.0)	-0.3 days (-1.0, 0.4)	-0.7 days (-3.2, 1.9)
Low dose CHO	0.0 days (-2.0, 2.0)	-0.3 days (-2.2, 2.9)	

Table 2.2 continued

	vs Fasting	vs Water/Placebo	vs Low dose CHO
Length of postoperative stay (continued)			
Subgroup analysis (continued)#			
Cardiac Surgery			
High dose CHO	-0.5 days (-3.4, 2.3)	0.4 days (-3.1, 3.9)	2.4 days (-2.5, 7.2)
Low dose CHO	-2.9 days (-7.8, 2.0)	-2.0 days (-5.4, 1.5)	
Postoperative complication rate**			
High dose CHO	1.0 (0.6, 2.0)	0.8 (0.6, 1.2)	1.0 (0.4, 2.5)
Low dose CHO	1.0 (0.4, 2.5)	0.8 (0.3, 2.0)	
Vomiting**			
High dose CHO	1.4 (0.7, 3.2)	1.2 (0.6, 2.4)	1.4 (0.6, 3.4)
Low dose CHO	1.0 (0.6, 1.7)	0.9 (0.3, 2.1)	
Insulin resistance#			
High dose CHO	-2.2 (-4.3, -0.09) †	-2.5 (-4.9, -0.2) †	-0.8 (-4.5, 2.9)
Low dose CHO	-1.4 (-4.9, 2.1)	-1.8 (-5.2, 1.7)	
Insulin sensitivity#††			
High dose CHO	1.2 ml/kg/min (-1.0, 3.4)	0.2 ml/kg/min (-0.7, 1.0)	
Nausea*††			
High dose CHO	-0.6 (-1.4, 0.07)	-0.7 (-1.1, -0.2) †	

Table 2.2 continued

	vs Fasting	vs Water/Placebo	vs Low dose CHO
Postoperative well-being*			
High dose CHO	0.1 (-0.2, 0.4)	-0.01 (-0.3, 0.2)	0.06 (-0.6, 0.7)
Low dose CHO	0.06 (-0.6, 0.7)	-0.01 (-0.8, 0.6)	
Postoperative fatigue*††			
High dose CHO	-0.08 (-0.7, 0.5)	0.1 (-0.3, 0.5)	
Return of intestinal function (time to first bowel motion#††)			
High dose CHO	-0.5 days (-1.6, 0.6)	-0.8 days (-2.0, 0.3)	

*Standardised mean difference (unit is standard deviations). †P < 0.05. ‡The standardised mean difference was converted back to a mean difference in days, using the standard deviations reported in the included trials. §The mean standard deviation (3.4 days) of all trials reporting major surgery (mean length of stay greater than 2 days) was used in this calculation, the mean length of stay in this group was 8.1 days. ¶The mean standard deviation (0.4 days) of all trials reporting minor surgery (mean length of stay less than 2 days) was used in this calculation, the mean length of stay in this group was 1.1 days. #Mean difference. **Odds ratio. ††No low dose CHO data available for this outcome. CHO = Carbohydrate. SD = Standard deviation.

Meta-regression also demonstrated no relationship between CHO dose and length of postoperative stay (Figure 2.6), with none of the heterogeneity in the model explained by the dose of carbohydrate administered (R^2 = 0) (Harbord and Higgins, 2008). Cumulative meta-analysis of high dose CHO versus control showed that further studies are unlikely to significantly change this effect estimate (Figure 2.7).

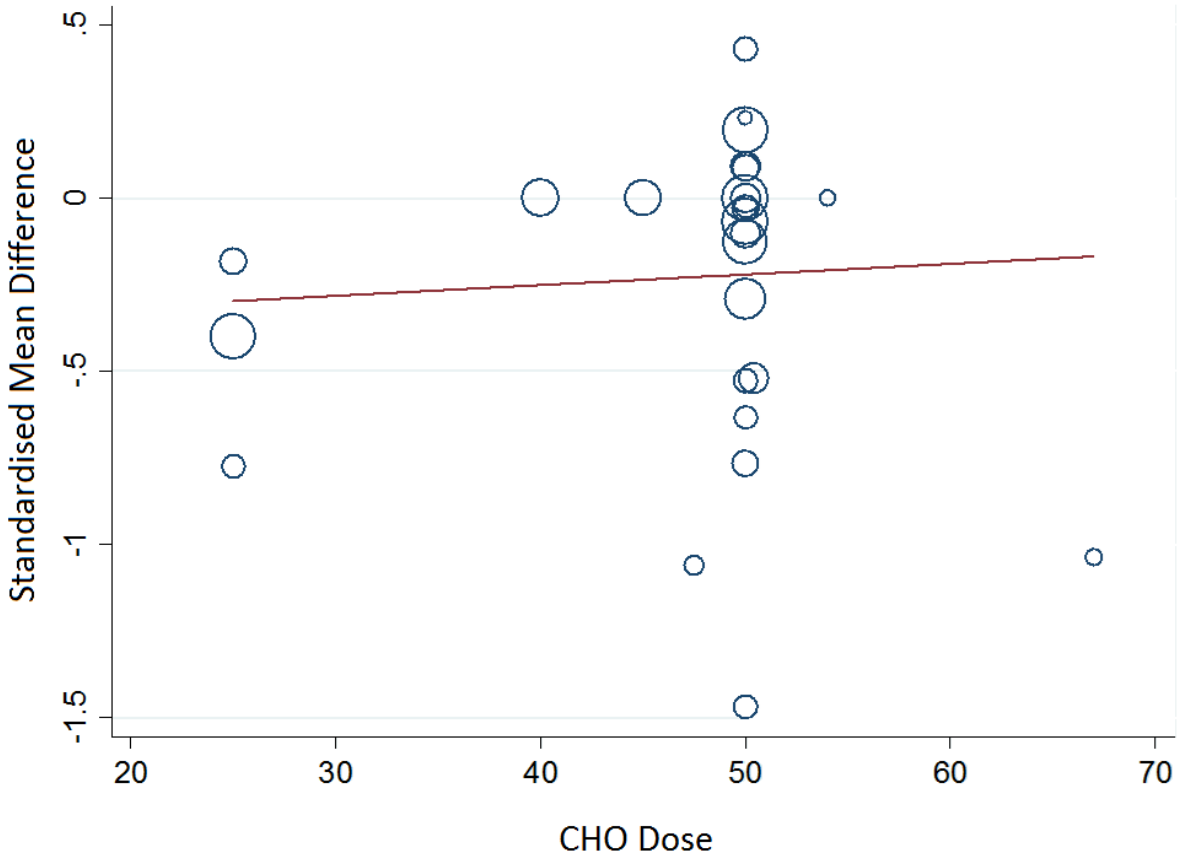

Figure 2.6 Meta-regression (Bubble Plot) for length of postoperative stay

The circles represent the effect estimate from each study, sized according to the precision of each estimate. The line of best fit (regression line) is almost horizontal, suggesting no relationship between CHO dose and length of postoperative stay.

CHO = Carbohydrate.

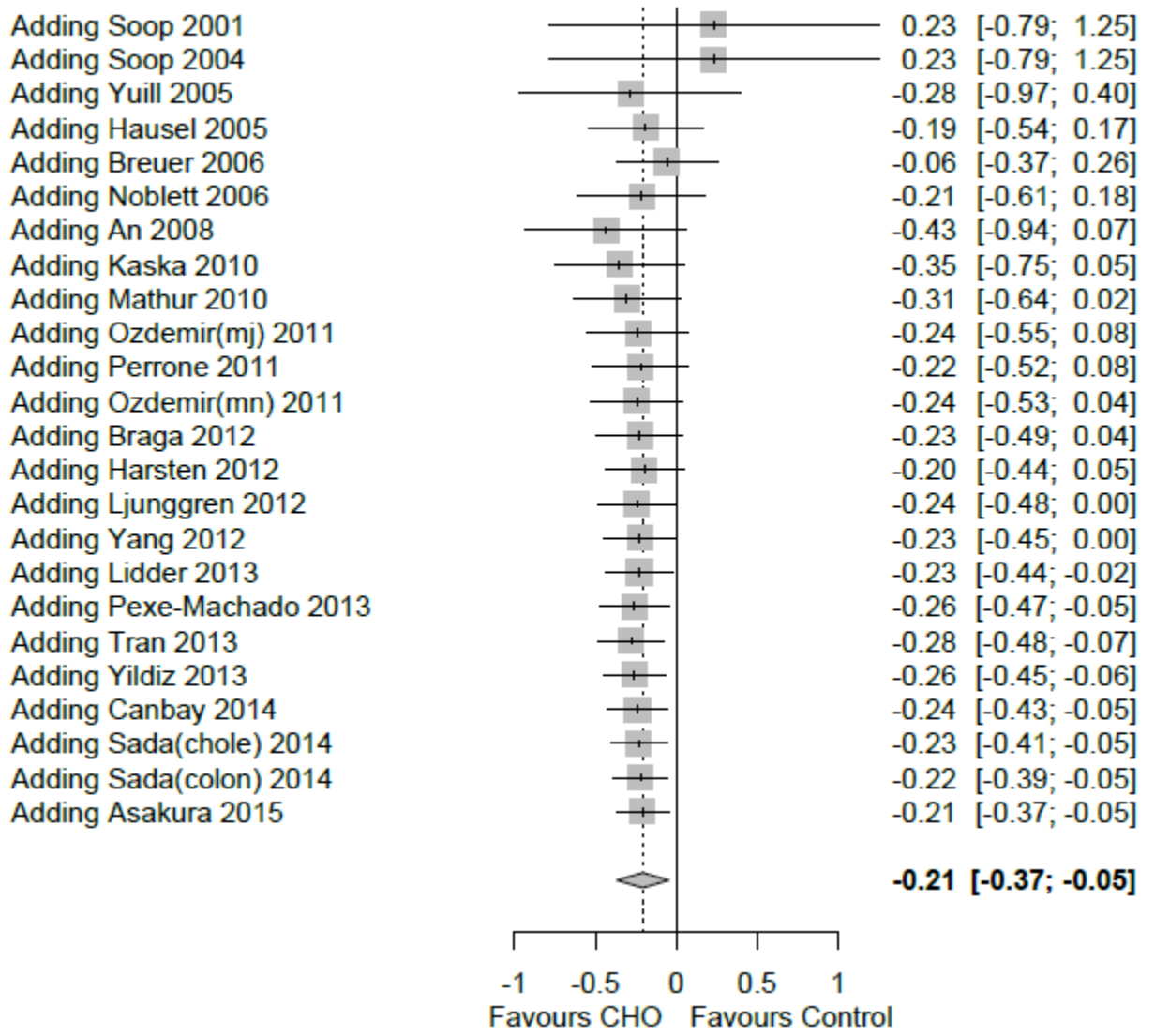

Figure 2.7 Cumulative meta-analysis (length of postoperative stay)

Trials comparing high dose carbohydrate loading with fasting, water or placebo.

CI = Confidence interval. (chole) = Cholecystectomy. (colon) = Colonic resection. (mj) = Major surgery. (mn) = Minor surgery. SMD = Standardised mean difference.

Testing for inconsistency between the direct and indirect evidence for this analysis yielded low inconsistency factors for all evidence loops, ranging from 0.06 to 0.4. There were also no significant differences between the results obtained using the direct evidence alone, the indirect evidence alone, and the combined network. All predictive intervals for the comparisons in this

analysis included zero, indicating moderate between-study heterogeneity. All sensitivity analyses showed similar results to the main analysis.

Subgroup analysis results are presented in Table 2.2. Except for two comparisons within the major abdominal surgery subgroup (defined as a mean length of postoperative stay of more than two days), none of the other subgroup comparisons showed a statistically significant difference. Inconsistency between the direct and indirect evidence for the major abdominal surgery subgroup was high (inconsistency factor of 2.4, with 95% CI up to 11.0), and all the predictive intervals in this subgroup included zero.

Visual inspection of a comparison-adjusted funnel plot for this outcome (Figure 2.8) suggests the presence of publication bias towards studies reporting a significant difference between the CHO groups and the controls.

2.4.3 Postoperative complications

This outcome was reported by seventeen studies, involving 1094 participants (Braga et al., 2012; Dock-Nascimento et al., 2012; Faria et al., 2009; Hausel et al., 2005; Kaska et al., 2010; Lidder et al., 2013; Mathur et al., 2010; Noblett et al., 2006; Perrone et al., 2011; Pexe-Machado et al., 2013; Soop et al., 2001; Soop et al., 2004; Tran et al., 2013; Yang et al., 2012; Yilmaz et al., 2013; Yuill et al., 2005; Zelic et al., 2012). All NMA comparisons for this outcome showed no statistically significant difference (Table 2.2).

Sensitivity analysis showed that exclusion of one trial with a much higher complication event rate than the other studies (Tran et al., 2013) did not significantly alter the results. Inconsistency analysis showed no evidence of a significant difference between the direct and indirect evidence for this outcome (inconsistency factors ranging from 0.3 to 0.96).

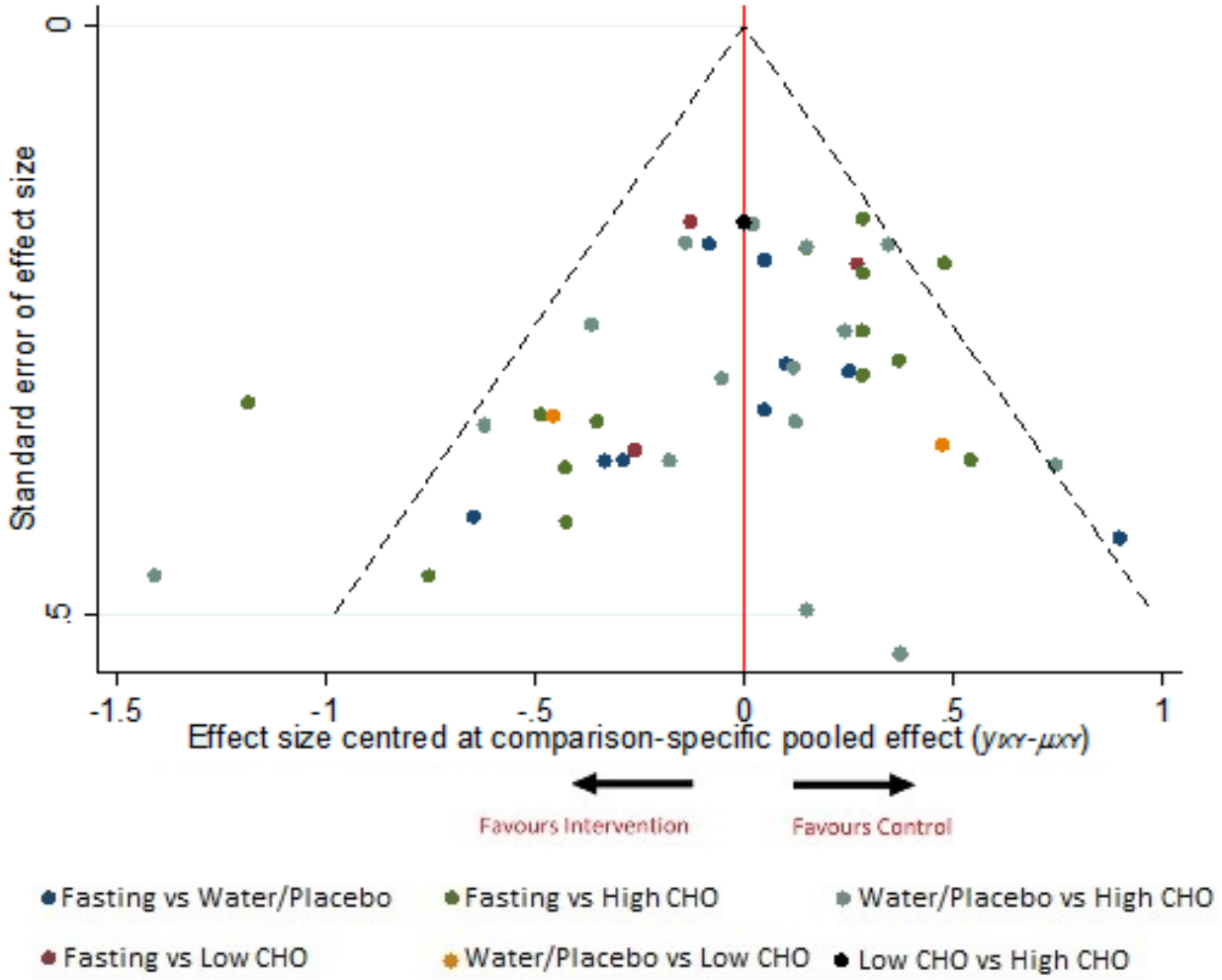

Figure 2.8 Comparison-adjusted funnel plot (length of postoperative stay)

The zero central line represents the null hypothesis that the study-specific effect sizes do not differ from the comparison-specific pooled estimates. Different coloured points on the plot represent the different comparisons, as in the key.

CHO = Carbohydrate.

2.4.4 Secondary outcomes

Aspiration pneumonitis

There were no aspiration pneumonitis events reported in any of the nineteen studies that reported this outcome (Aronsson et al., 2009; Bisgaard et al., 2004; Canbay et al., 2014; Dock-Nascimento et al., 2012; Itou et al., 2012; Jarvela et al., 2008; Lidder et al., 2013; Mathur et al., 2010; Meisner et al., 2008; Noblett et al., 2006; Perrone et al., 2011; Raksakietisak et al., 2014; Soop et al., 2001;

Soop et al., 2004; Tran et al., 2013; Wang et al., 2010; Yang et al., 2012; Yildiz et al., 2013; Yuill et al., 2005) therefore NMA was not performed.

Vomiting

Eight studies (Bisgaard et al., 2004; Faria et al., 2009; Feguri et al., 2012; Hausel et al., 2005; Itou et al., 2012; Jarvela et al., 2008; Raksakietisak et al., 2014; Yang et al., 2012) reported the rate of postoperative vomiting, involving 820 participants. NMA results are summarised in Table 2.2. There were no statistically significant differences between the groups in the network. Inconsistency for this analysis was low (inconsistency factor of up to 0.4).

Insulin resistance

Thirteen studies (Canbay et al., 2014; Chen et al., 2014, 2015; Dock-Nascimento et al., 2012; Faria et al., 2009; Feguri et al., 2012; Mathur et al., 2010; Perrone et al., 2011; Pexe-Machado et al., 2013; Rapp-Kesek et al., 2007; Tran et al., 2013; Wang et al., 2010; Yang et al., 2012) measured insulin resistance using the HOMA-IR method, involving 503 participants. Table 2.2 shows the NMA results for all the comparisons in this network. High dose CHO administration resulted in a statistically significant decrease in insulin resistance compared to fasting, and water or placebo, but with wide confidence intervals approaching non-significance. One study (Wang et al., 2010) reported very different numerical results compared to all other trials, despite reporting the same methodology and formulae. Sensitivity analysis excluding this study showed no statistically significant differences between any of the groups. Inconsistency in this network was high (inconsistency factors of 2.4 and 4.8).

Insulin sensitivity

Four studies (Ljunggren et al., 2014; Ljungqvist et al., 1994; Soop et al., 2001; Soop et al., 2004) involving 62 participants measured insulin sensitivity using the hyperinsulinaemic-euglycaemic clamp method. No low dose CHO studies were available for this outcome. NMA showed no significant difference in any of the comparisons (Table 2.2).

Nausea

This was reported by four studies (Hausel et al., 2005; Karlsson et al., 2016; Mathur et al., 2010; Sada et al., 2014) with data available on 423 participants. All used a visual analogue scale. NMA

showed that administration of high dose CHO resulted in a moderate reduction in nausea (0.7 SD [SMD, 95% CI 0.2 – 1.1]) compared with water or placebo, but no statistically significant difference when compared with fasting (Table 2.2). All predictive intervals for this analysis included zero (no significant difference). Sensitivity analysis (reported vs imputed data) showed that exclusion of one study (Sada et al., 2014) resulted in no statistically significant findings between high dose CHO and either control treatment node.

A further study (Singh et al., 2015) reported this outcome at various postoperative time points in a three-arm RCT comparing preoperative fasting, oral placebo and oral low dose CHO. This could not be incorporated in the NMA as the authors reported only a mean incidence count at each time point. They found no statistically significant difference at time points beyond 12h after surgery.

Postoperative well-being

This was reported by six studies (Asakura et al., 2015; Bisgaard et al., 2004; Henriksen et al., 2003; Ljunggren and Hahn, 2012; Mathur et al., 2010; Meisner et al., 2008), most using a visual analogue scale, with data available on 443 participants. NMA found no significant difference between the groups in any of the comparisons (Table 2.2). The inconsistency factor for this analysis was low (0.2).

Postoperative fatigue

Six studies (Bisgaard et al., 2004; Harsten et al., 2012; Henriksen et al., 2003; Lauwick et al., 2009; Mathur et al., 2010; Yildiz et al., 2013) reported postoperative fatigue scores using a visual analogue or ten-point ordinal scale, with data available on 576 patients. None of the studies investigating low dose CHO reported this outcome. There were no significant differences in any of the comparisons within the network (Table 2.2).

Return of intestinal function

Two studies (An et al., 2008; Noblett et al., 2006) reported time to passage of flatus, so there were insufficient data to perform NMA. One (An et al., 2008), involving 51 patients, reported a reduction of 0.4 days in the time to postoperative passage of flatus in patients given high dose CHO compared to patients who were fasted before surgery. The other study (Noblett et al., 2006)

was a three-arm trial (high dose CHO, water and fasting) that found no significant difference between the groups.

Two studies (Noblett et al., 2006; Ozdemir et al., 2011) reported time to passage of first bowel motion, with one (Ozdemir et al., 2011) reporting the outcome for patients undergoing major and minor abdominal surgery separately. Both studies investigated high dose CHO administration compared with fasting and water in a three-arm design. NMA showed no significant differences between the three groups (Table 2.2).

2.5 Discussion

This NMA shows that administration of a preoperative CHO load within four hours of surgery start time led to a small reduction in length of postoperative stay when compared to fasting, but no significant effect compared to allowing patients water or a placebo drink before surgery. Heterogeneity analysis for this outcome using predictive interval calculations showed moderate between study heterogeneity, and evidence of publication bias was suggested on examination of the comparison-adjusted funnel plot. Further, sensitivity analysis splitting the water/placebo node, then the placebo subgroup into blinded and un-blinded studies showed no significant difference between any of the placebo groups and the CHO groups. In addition, cumulative MA of this outcome also suggests that future studies are unlikely to show a larger effect than in this review.

SMD was used for length of postoperative stay to account for the wide variety in expected length of stay between the different procedures. Procedures with differing expected lengths of stay cannot be directly compared using MD as any effect of CHO administration could be expected to be proportional to the actual length of stay. SMD can be interpreted using rules of thumb (Higgins and Green, 2011) where an SMD of 0.4 SD or less is considered to indicate a small effect, suggesting that the difference found between the CHO and fasting groups was small. The back-transformation results support this conclusion, showing a reduction in length of stay of approximately 10% in both CHO groups compared to fasting. It is important not to conclude from the subgroup analysis that the effect of preoperative CHO loading on major abdominal surgery is larger than on other procedures as the relative reduction in length of stay was similar between subgroups (Sun et al., 2014).

This review found no evidence that high dose CHO was more or less effective in reducing length of stay compared to low dose CHO. Available data for low dose CHO in the network were much fewer, highlighted by wider confidence intervals than the high dose CHO comparisons. Sensitivity analysis using meta-regression supported this finding, showing no evidence of a CHO dose-response relationship.

There was no significant difference in the postoperative complication rate for patients given a CHO load compared to patients who remained fasted or those who were given water or a placebo drink. Although high dose CHO conferred a reduction in nausea scores at 24 hours compared to water or placebo, this was based on a small number of studies and there was no statistically significant difference in the incidence of vomiting between the groups. No other significant differences were found between the CHO and control groups in any of the other clinical secondary outcomes investigated. The confidence intervals for some of these outcomes were wide however, reflecting a relative paucity of available data and heterogeneity. No instances of aspiration pneumonitis were reported in any of the trials.

The effect of CHO loading on postoperative insulin resistance was investigated as it is this effect in particular that provided the rationale for introducing preoperative CHO loading (Ljungqvist et al., 2002; Nygren et al., 1998). There was no statistically significant difference in insulin sensitivity (measured by the gold standard hyperinsulinaemic-euglycaemic clamp method) in this NMA. This may however be a type II error (false negative finding) as only four studies were available to assess insulin sensitivity. Further, a statistically significant difference in insulin resistance (measured by homeostatic modelling) between high dose CHO and both control treatment groups was found, though with high inconsistency, and sensitivity analysis suggesting this finding was influenced by the reported results of a single study (Wang et al., 2010). A reduction in postoperative insulin resistance *per se* may not be clinically important unless it in turn leads to improved postoperative outcomes.

Three previous MAs have investigated the effect of preoperative CHO loading (Awad et al., 2013; Li et al., 2012; Smith et al., 2014). The findings of this present review are broadly consistent with the largest and most recent of these (Smith et al., 2014), which included 27 trials and found a small

decrease (0.4 days) in length of postoperative stay for patients given a CHO load (high dose) only when compared to fasting, an increase in insulin sensitivity compared to the control treatments and a shorter time to passage of flatus by less than half a day. No other significant differences were found for an identical set of outcomes as this review.

This is the first review on this subject to use NMA methodology. This has allowed the incorporation of more data than all previous reviews and the use of all the direct and indirect evidence available, thereby increasing the precision of the effect estimates. The fasting, water/placebo and CHO dosing regimens were also analysed simultaneously as separate groups in a manner that fully respects randomisation (Caldwell et al., 2005), unlike subgroup analysis (Sun et al., 2014), thus eliminating an important source of clinical heterogeneity and bias in previous MAs. This increases the external validity and applicability of these results. The review process and quality assessment were conducted in accordance with the Cochrane Collaboration's recommended standard methodology (Higgins and Green, 2011) and the PRISMA guidelines for NMA (Hutton et al., 2015).

There are some potential limitations to this study. Firstly, the validity of the results of any MA is dependent to a large degree on the quality of included trials, and most trials were of low to moderate quality with the risk of performance and selection bias being of particular concern. A lack of well-designed, placebo controlled trials in particular led to the combination of placebo and water into one group for the main analysis. This issue was addressed through sensitivity analysis by splitting the groups, which did not show significantly different results. Secondly, there was evidence of moderate statistical heterogeneity and inconsistency between the direct and indirect evidence for some outcomes. This is to be expected given the heterogeneity in trial design, endpoints measured and clinical settings. Nevertheless, subgroup and sensitivity analyses to explore this heterogeneity did not reveal significantly different results. Thirdly, comparisons involving low dose CHO administration for some outcomes were informed by only one or two head-to-head RCTs, with the majority of data derived from indirect evidence. Although this may affect the power and reliability of those effect estimates (Mills et al., 2013), all the results for high dose CHO administration were comparable, suggesting that the true effect of low dose CHO administration is likely to be similar to this review's estimates.

Current anaesthetic guidelines recommend allowing patients clear fluids up to two hours before surgery (American Society of Anesthesiologists, 2011; Smith et al., 2011), based on the established safety of this practice in patients who are not at high risk of aspiration (Brady et al., 2003). Recently published ERAS guidelines strongly recommend the routine use of oral carbohydrate loading before a variety of elective procedures including colonic resection (Gustafsson et al., 2013), rectal/pelvic surgery (Nygren et al., 2013), gastrectomy (Mortensen et al., 2014), pancreaticoduodenectomy (Lassen et al., 2012) and radical cystectomy (Cerantola et al., 2013). This is despite an acknowledgement that the evidence supporting this recommendation is of low to moderate quality, and for some procedures only by extrapolation (Cerantola et al., 2013; Lassen et al., 2012; Mortensen et al., 2014). This review, incorporating the results of over 40 RCTs and involving over 3000 patients, shows that the administration of preoperative CHO within four hours of surgery start time is safe but may not provide a clinically relevant benefit over water or a flavoured drink with no calories. This needs to be considered when developing elective ERAS protocols, particularly given the costs involved in routine CHO loading. Future trials investigating preoperative loading should focus on the potential role of other additives in selected patients.

2.6 Conclusion

This review represents the most comprehensive synthesis of the available evidence to date, and demonstrates the utility of NMA in synthesising surgical RCT data when different control treatments have been used. It shows that CHO loading before elective surgery confers a small reduction in length of stay when compared to fasting, but no significant difference when compared to water or placebo. No other clinically relevant effect on post-operative outcomes was found.

Therefore, current RCT evidence does not support routine preoperative CHO loading for adults undergoing elective surgery. This is acknowledged in the latest ERAS guidelines by the Society of American Gastrointestinal and Endoscopic Surgeons, and the American Society of Colon and Rectal Surgeons (Carmichael et al., 2017), which reference this study.

CHAPTER THREE

Systematic review and network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults

Review protocol registered with PROSPERO (Appendix A2)

Published in the British Journal of Surgery (Appendix A3):

Amer, M.A., Smith, M.D.[1], Khoo, C.H.[1], Herbison, G.P.[2], and McCall, J.L.[1] (2018). Network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults. BJS *105*, 1398-1407

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My contribution to this chapter

This project was conceived by my supervisors (JLM, MDS and GPH) with contributions from myself. I designed the search strategy, drafted and completed the registered version of the review protocol (Amer et al., 2014) with revisions in conjunction with my supervisors. I performed the systematic search, selected and extracted data from eligible trials (with co-author duplication by CHK and MDS) and performed all of the analysis with expert advice from GPH. All drafts and the final manuscript of the resulting publication were written by myself, with revisions in conjunction with my supervisors and journal reviewers. This chapter is adapted from the published paper (Amer et al., 2018).

3.1 Chapter summary

Proton pump inhibitors (PPI) are the mainstay of treatment for GORD, but are associated with ongoing cost and side effects. Anti-reflux surgery is cost-effective, and is preferred by many patients. A total (360^{o} 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 MAs have compared some of these procedures but there is ongoing uncertainty about which, if any, is superior. NMA allows

for multiple simultaneous comparisons and robust synthesis of the available evidence in these situations. An NMA comparing all anti-reflux procedures was performed, to identify which has the most favourable outcomes at short (3 – 12 months), medium (1 – 5 years) and long-term (6 – 10 years, and > 10 year) follow-up. Article databases were systematically searched for all eligible RCTs. Primary outcomes were quality of life measures and dysphagia. Secondary outcomes included reflux symptoms, pH studies and complications. NMA was performed using Stata 13.1 routines. Fifty one RCTs were included, involving 5357 patients, and fourteen different treatments. Posterior partial fundoplication (PPF) ranked best in terms of control of reflux symptoms, and caused less dysphagia compared to most other interventions including Nissen fundoplication. This was consistent across all time-points and outcome measures. This study shows that PPF provides the best balance of long-term, durable reflux control with less dysphagia, compared to other treatments. PPF should be considered the standard intervention for the surgical management of GORD in adults.

3.2 Introduction

GORD affects up to 20% of the population in the Western world (Dent et al., 2005). PPI therapy has been the mainstay of treatment for GORD for the last twenty years, with surgery reserved mainly for patients with refractory GORD (Wileman et al., 2010). However the cost, inconvenience and potential side effects of long-term acid suppression mean many patients prefer surgery (Broeders et al., 2010; Grant et al., 2013), and several recent RCTs have confirmed the long-term cost-effectiveness of surgical intervention compared with continued medical therapy (Anvari et al., 2011; Faria et al., 2013; Goeree et al., 2011; Grant et al., 2013). Surgical procedures for GORD largely involve a fundoplication, or the creation of a flap valve and higher pressure zone, by wrapping the gastric fundus around the gastro-oesophageal junction (Mackay et al., 2010). Several variations of this are commonly performed including a total (360^{o} or Nissen) fundoplication (NF) (Nissen, 1956), and partial fundoplications 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 and other obstructive side effects following fundoplication, but the potential down-side is poorer reflux control (Stefanidis et al., 2010).

More than fifty RCTs have compared various fundoplication procedures, involving thousands of patients and years of follow-up data. Although many have been pooled in pairwise MAs, all these MAs have inherent limitations as they have either combined different fundoplication techniques together to allow a head-to-head analysis (Broeders et al., 2011; Ma et al., 2012; Memon et al., 2015; Varin et al., 2009), or compared only two techniques in isolation (Broeders et al., 2010; Broeders et al., 2013; Shan et al., 2010; Tan et al., 2011). It therefore remains difficult more than 40 years after the first RCT was published (Demeester et al., 1974), to determine which fundoplication technique is superior both in terms of reflux control and potential harms (Fuchs et al., 2014). Some calls have been made for even more RCTs (Thompson and Watson, 2015), while others have suggested that the choice of procedure should be left to the surgeon as it is not possible to determine which technique is best (Daud et al., 2015; Stefanidis et al., 2010).

NMA allows for simultaneous comparison and ranking of multiple different treatments for a given condition, as explained in Chapter 1. This chapter details the results of a systematic review and NMA comparing all anti-reflux procedures subjected to RCT evaluation in adults with GORD, to identify which 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 can change considerably over time following surgery, data from four different follow-up time points (3-12 months, 1-5 years, 5-10 years and over 10 years) were analysed separately.

3.3 Methods

This study was conducted in accordance with the Cochrane Collaboration's recommended methodology (Higgins and Green, 2011) and PRISMA guidelines (Moher et al., 2009), including those specifically concerning NMA (Hutton et al., 2015). The study protocol was prepared and published *a priori* (Amer et al., 2014).

3.3.1 Search strategy and selection criteria

All randomised and quasi-randomised clinical trials that compared surgical procedures (laparoscopic or open) for the treatment of GORD or a surgical procedure with best medical treatment with PPIs were included.

Studies that enrolled adult participants with an established diagnosis of GORD based on symptoms and an objective measure such as endoscopy or pH manometry, and who were deemed appropriate for surgical management, were included. Studies that included patients with established Barrett's or extra-oesophageal symptoms only were excluded.

Trials assessing endoscopic treatment of GORD were excluded. Non-fundoplication procedures, including those discontinued because of safety concerns (Kmiot et al., 1991) were included, but subjected to sensitivity analysis. Interventions with other variations such as different wrap lengths, omission of a hiatoplasty or fixation to the right hiatal pillar as part of the procedure, were permitted, but such variations were noted. Interventions involving fundoplication in combination with another procedure (such as Heller's myotomy for achalasia) were excluded. Authors of published trials were contacted for clarification when randomisation status was not clear.

The following article databases and grey literature sources were searched, using a structured search strategy (Appendix C1), to identify eligible trials:

1. The Cochrane Central Register of Controlled Trials (CENTRAL), to March 2017
2. MEDLINE (1966 to March 2017).
3. EMBASE (1980 to March 2017).
4. Web of Science (1945 to March 2017).

No language, publication status or year of publication restrictions were applied. All citations were in English, as translated by the databases. Abstracts and full texts in French, German and Japanese were able to be translated by the data extractors. Studies in other languages were translated using Google translate (Jackson et al., 2019). The search strategy was developed in consultation with an expert health librarian using a combination of subject headings and free text terms relating to the surgical treatment of GORD. The Cochrane sensitivity maximising search strategy was used to search for RCTs in MEDLINE (Higgins and Green, 2011). The British Medical Journal's EMBASE Randomised Controlled Trial Strategy was used to search for RCTs in EMBASE (BMJ, 2017).

The reference lists of all eligible studies and of reviews of the topic were also hand-searched to identify any additional studies. Experts in the field were contacted to identify any unpublished research or ongoing trials.

In addition, the World Health Organisation's International Clinical Trials Registry Platform and clinicaltrials.gov were searched to identify ongoing trials. Contact authors were then approached by letter or email requesting any available information to date.

The results of searches from both the electronic databases and other resources were combined in a spreadsheet. Duplicate citation records and publications were excluded. Multiple publications of the same trial were retained in case different outcome data were reported in each. Two authors independently screened all titles and abstracts for eligibility. The full text of potentially eligible trials were subsequently obtained and reviewed against the pre-defined inclusion criteria. Any exclusions at this point were independently recorded (together with the reason for exclusion) before a final list of included trials was drawn up. Disagreements were resolved by discussion and consensus, and arbitration by a third author when required.

3.3.2 Outcome measures

Trials that reported any of the following outcomes were included.

Primary outcomes:

1. General/health-related quality of life scores, measured on an appropriate validated tool. A higher value indicated better quality of life.
2. GORD/gastrointestinal-specific quality of life scores, measured on an appropriate validated tool. A higher value indicated better quality of life.
3. Dysphagia, measured either as a dichotomous variable or on a validated scale (such as Dakkak). A higher scale value indicated less dysphagia (as per Dakkak's original description (Dakkak and Bennett, 1992)).

Secondary outcomes:

1. Reflux symptoms, measured as a dichotomous variable or on a patient-reported scale. A higher scale value indicated more reflux.

2. Oesophageal acid exposure, measured as a DeMeester score or similar. A higher value indicated more acid exposure.
3. Total oesophageal acid exposure time (as a percentage) on pH monitoring. A higher value indicated a longer acid exposure time.
4. Dilatation for dysphagia rate, defined as the need for oesophageal dilatation for symptomatic dysphagia postoperatively.
5. Reoperation rate, defined as the number of patients who required revision surgery for ongoing symptoms, severe dysphagia and/or objective findings of persistent GORD during follow-up.
6. Postoperative complications as defined by the trial authors.
7. Gas bloat syndrome (Walker et al., 1992), measured as a dichotomous variable or on a patient-reported scale. A higher value indicated more gas bloat. Data on hyper-flatulence, epigastric pain or abdominal bloating in isolation were not considered indicative of gas bloat syndrome and were not included.

For each of these outcomes, different scales with an opposite direction of severity were inverted by subtracting the mean from the maximum possible value for the scale, to ensure all scales point in the same direction (Higgins and Green, 2011).

Composite patient satisfaction scores (such as Visick) were not used as these do not specify which symptom patients are suffering from, and so cannot be used to assess reflux or dysphagia, and are not validated quality of life assessment tools. Similarly, gastrointestinal symptom rating scale scores were only used when subscores for reflux were reported separately.

3.3.3 Data extraction and quality assessment

A structured, pre-piloted data extraction form based on the Cochrane Collaboration's Data Collection Form Template (Cochrane, 2013) was used by two authors to independently extract and record data, including study design, patient and intervention characteristics and outcome data (Appendix C2). Continuous (score) and dichotomous (rate) data for each outcome were both included and recorded separately. For all primary outcomes and all secondary outcomes except postoperative complications data were collected and analysed separately in four groups according to follow-up time, where enough data were available to make this meaningful:
1. From 3 months, up to and including 1 year.

2. From over 1 year, up to and including 5 years.
3. From over 5 years, up to and including 10 years.
4. Over 10 years.

Where one trial reported the same outcome for different follow-up time points, data were included in the appropriate groups ensuring that duplication was avoided. Where trials reported two sets of data for the same outcome within the same time point (such as three years and four years), the most recent data (four years in this example) were included.

Discrepancies were resolved by discussion with arbitration by a third author when required. Requests for further data were made when required by emailing the contact author of the relevant trial, where an email address was available.

Where data were missing or not available, study authors were contacted to request this, where an email address was available. Missing statistics such as standard deviations were calculated from reported data where possible (Higgins and Green, 2011; Hozo et al., 2005). When standard deviations could not be calculated and attempts to contact study authors were exhausted, these were imputed using the reported standard deviations from other trials that used the same measure/scale where possible. Sensitivity analysis was performed to explore the effect of imputed versus reported data.

Where trials used a combination of different surgical techniques (i.e. more than one type of fundoplication) in one arm, individual patient data were sought where this was not reported. If this was not available, the trial was excluded. The review protocol had stated that such trials would be included in the analysis if more than 80% of patients in the affected arm of the study underwent the same single procedure, but no such instances were encountered.

The methodological quality of each included study was independently assessed by two authors as part of the data extraction process. This was based on the Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011), using the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and any other potential sources of bias (such as

baseline imbalances or differential diagnostic activity). Each domain was assessed as low risk, high risk, or unclear. Disagreements were resolved by discussion and arbitration by a third author where consensus could not be reached.

3.3.4 Statistical analysis

A random-effects NMA was performed using the suite of specific Stata (StataIC 13, StataCorp LP., College Station, Texas) routines available for this (Chaimani et al., 2013; Chaimani and Salanti, 2015; White, 2015). The main analysis comprised up to 14 treatment groups representing the treatments for which data were available for that outcome and follow-up time point, with PPI allocated as the reference treatment. Fundoplications were divided into groups as follows:

1. Total (360^{o}) or Nissen fundoplication (with or without the division of the short gastric arteries, and with or without the use of a bougie).
2. 90^{o} fundoplication.
3. Anterior partial fundoplication (APF, 120^{o} or more).
4. Posterior partial fundoplication (PPF, 180^{o} or more).

Where no data for PPI were available, a fundoplication technique (90^{o}, APF, PPF) was instead allocated as the reference, in that order. Network maps for each outcome were produced to provide a visual summary of the network of evidence available.

For outcome time points with data available from five RCTs or more, and statistically significant differences between the treatments, the probability of each fundoplication technique (and PPI, as the reference) ranking as the best, second, third, fourth or worst treatment in the network was calculated, and presented as a rankogram. Rankings were otherwise not calculated to avoid over-interpretation (Dias et al., 2012). Where enough data were available, the ranking scores (surface under the cumulative ranking curve (SUCRA)) 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 between the treatments.

For each comparison between different techniques, continuous data were summarised as an MD (with units) or SMD (expressed as SD), as appropriate, with 95% CI. An SMD was used when studies assessing the same outcome used different measures or scales which were not possible to

compare directly. Categorical data were summarised as odds ratios with 95% CI. An intention-to-treat analysis was used.

The following sensitivity analyses were performed for all individual outcome time point analyses where possible. Firstly, the analysis was rerun excluding all non-fundoplication procedures (but including PPI as the reference treatment where possible). Secondly, the Nissen node in the fundoplication/PPI analysis (above) was split into up to four nodes according to whether a bougie was used or not and whether the short gastric vessels were preserved or divided, to address the heterogeneity of that node. Studies that used Nissen fundoplication but did not specify these variables were excluded from this analysis, whereas studies that compared two such Nissen variations (and were therefore excluded from the main analysis) were included. Thirdly, the influence of imputed versus reported data was assessed by excluding studies where data were imputed and comparing the results with the main analysis. Post-hoc sensitivity analysis was also performed for the dysphagia and reflux networks by serially excluding trials that included a PPF arm, to assess whether one trial significantly influenced the results, and by moving 120 degree fundoplication from the APF node to the 90^{o} fundoplication node. Sensitivity analysis results were reported if they were significantly different from the main analysis results.

Statistical heterogeneity was assessed by calculating predictive intervals (Chaimani et al., 2013). Inconsistency in the evidence structure was also assessed (Dias et al., 2010) by calculating the difference between the direct and indirect estimates (the inconsistency factor) in each closed loop formed by the network of trials. Any significant inconsistencies were investigated further to determine possible causes, where enough data were available. Publication bias was assessed by visual inspection of comparison-adjusted funnel plots (Chaimani et al., 2013) for primary outcomes with sufficient data.

3.4 Results

3.4.1 Search results and study characteristics

The database search and study selection process is summarised in Figure 3.1. Fifty one RCTs (reported in 77 papers with eligible data) were included, involving 5357 patients, and 13 different

surgical procedures in addition to PPIs (Table 3.1). The most common comparison was NF versus PPF, and NF was compared to every other fundoplication in at least three RCTs.

Table 3.2 details the characteristics and relevant outcomes of each included RCT, and Table 3.3 summarises the number of trials and patients for which data were available for each outcome and follow-up time point.

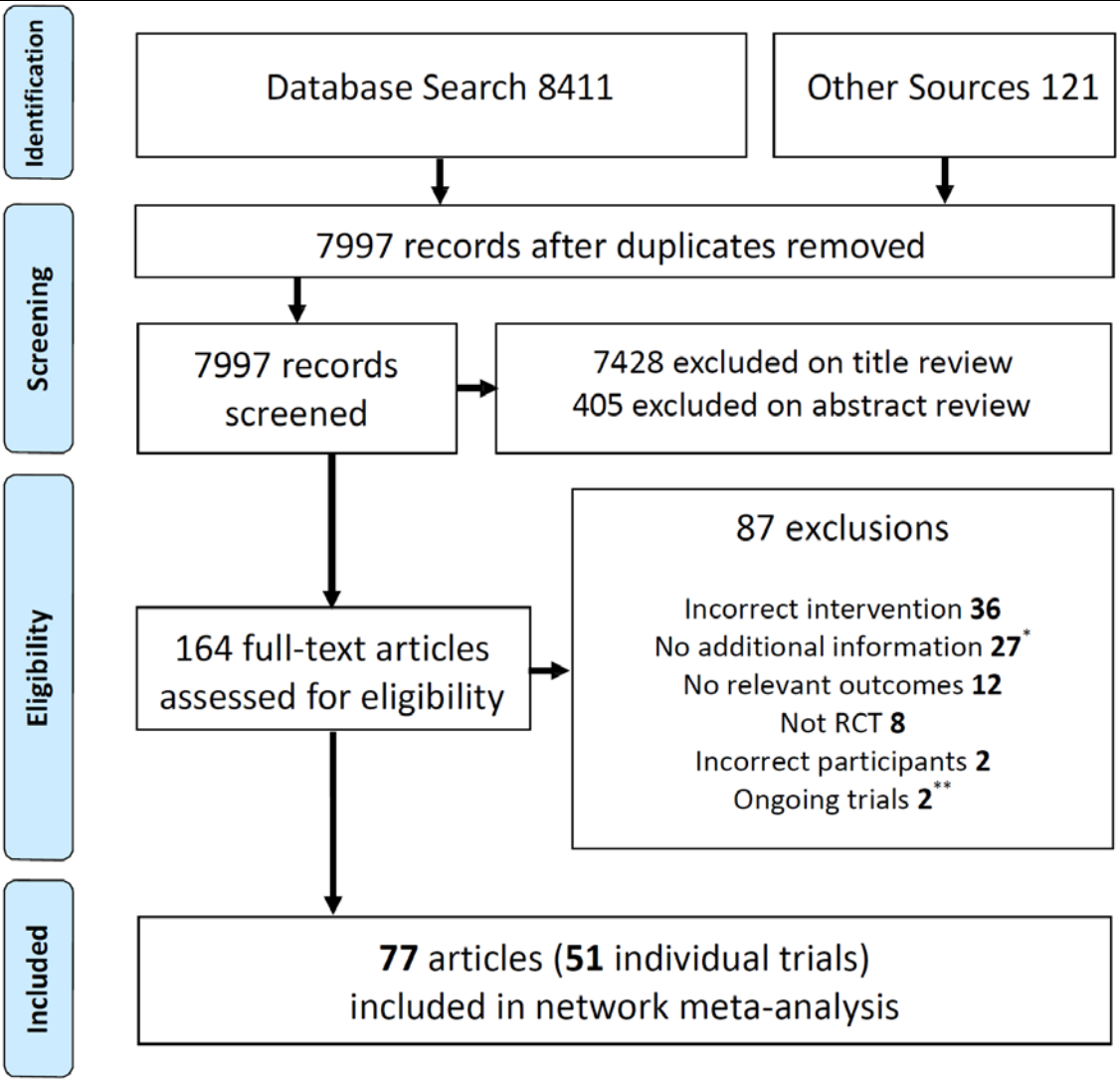


Figure 3.1 Systematic search and study selection flowchart

* Includes duplicate publications, and papers reporting results for an included trial with no additional relevant data

** No data currently available from contacted trial investigators

Table 3.1 Summary of included trials

	Trials*	Patients†	Publication year‡	Trial Location			
				Europe	Americas	Oceania	Asia/Africa
Nissen vs. PPF	19	2153	1989 – 2015	14	2		3
Nissen vs. APF	6	530	2004 – 2016	3		1	2
Nissen vs. 90^{o} fundoplication	3	225	1989 – 2012	1		2	
Nissen vs. PPI	3	803	2008 – 2011	2	1		
PPF vs. APF	4	339	2007 – 2017	3		1	
PPF vs. 90^{o} fundoplication	1	32	1989	1			
Nissen vs. Angelchik	3	163	1984 - 1994	3			
Nissen vs. Hill	2	132	1974 - 2012		2		
Nissen vs. Other§	7	706	1974 - 2015	4	3		
PPF vs. FND 360^{o}	1	252	2012		1		
NSGVD vs. NSGVP	6	438	1999 – 2009	4	1	1	
Bougie vs. no bougie¶	1	171	2000		1		
BM IV vs. Hill repair	1	30	1974		1		

*The number of trials reporting this comparison. Three arm trials are therefore included three times in this table, to account for all three direct pairwise comparisons in them. †The total number of patients randomised 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 each trial's index paper was published. Subsequent follow-up papers were included in this review, but are not included in this column. §Single trial comparisons. 'Other' included the following procedures: Belsey Mark IV; Roux-en-Y duodenal diversion; cardia calibration with posterior gastropexy; Nissen with mesh hiatoplasty; Nissen with fascial graft; fixed 'non-deformable' 360 degree fundoplication; mesh hiatoplasty and cardiophrenicopexy. ¶Nissen with, and without a bougie for calibration.
APF = Anterior partial fundoplication. BM IV = Belsey Mark IV. FND 360^{o} = Fixed 'non-deformable' 360^{o} fundoplication. NSGVD = Nissen with short gastric vessel division. NSGVP = Nissen with short gastric vessel preservation. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.2 Characteristics of included trials

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Anvari et al., 2006, 2011)	Canada	Nissen (SGVD, NB) vs. PPI	QOL; pH<4; Complications - 1 and 3 years Dysphagia (cont); Reflux (cont) - 1 year	104
(Aye et al., 2012)	USA	Nissen (SGVD, B) vs. Hill repair	GQOL; Dysphagia (cont); DMS; pH<4; Dilatations; Reoperations; Complications - 1 year	111
(Baigrie et al., 2005; Broeders et al., 2012; Roks et al., 2017a)	South Africa	Nissen (SGVP, B) vs. APF	Dysphagia (cont and dich); Reflux (cont) - 1, 5 and 12 years Dilatations; Reoperations - 5 and 12 years GBS (dich) - 12 years	163
(Blomqvist et al., 2000; Mardani et al., 2009)	Sweden	Nissen (SGVP, B) vs. Nissen (SGVD, B)	QOL; Dysphagia (dich); Reflux (cont and dich); GBS (dich); Complications - 1 and 10 years Dysphagia (cont) - 10 years GQOL; pH<4; Reoperations - 1 year	99
(Booth et al., 2008)	UK	Nissen (SGVD, D) vs. PPF	Dysphagia (dich); Reflux (dich); Dilatations; Complications - 1 year	127

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Bouillot et al., 1999)	France	Nissen (SGVD, NS) vs. PPF	Dysphagia (dich); Reflux (dich); Complications - 1 year	45
(Cao et al., 2012)	China	Nissen (SGVP, NB) vs. APF	Dysphagia (cont); Reflux (cont); DMS - 1, 2 and >5 years Reflux (dich); Reoperations - >5 years	100
(Chrysos et al., 2001)	Greece	Nissen (SGVD, B) vs. Nissen (SGVP, B)	Dysphagia (dich); Reflux (dich); DMS; GBS (dich); Complications - 1 year	56
(Chrysos et al., 2003)	Greece	Nissen (SGVP, NB) vs. PPF	Dysphagia (dich); Reflux (dich); DMS; Dilatations; GBS (dich); Complications - 1 year	33
(Chrysos et al., 2004)	Greece	Nissen (SGVP, NB) vs. APF	Reflux (dich) - 5 months	24
(Csendes et al., 2000)	Chile	Nissen (SGVD, NS) vs. Cardia calibration with posterior gastropexy	pH<4; Reoperations - >1 year	164

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Demeester et al., 1974)	USA	Nissen (NS, B) vs. Belsey Mark IV vs. Hill	Dysphagia (dich); Dilatations; Complications - 5 months	45
(Djerf et al., 2016)	Sweden	Nissen (NS) vs. APF	QOL; Dysphagia (cont); Reflux (cont); pH<4; Reoperations - 1 and 10 years	72
(Farah et al., 2007)	Brazil	Nissen (SGVP, NB) vs. Nissen (SGVD, NB)	Dysphagia (dich); Reflux (dich); Dilatations; Complications - 1 year	90
(Ferulano et al., 2000)	Italy	Nissen (SGVP, NS) vs. PPF	Dysphagia (dich); Reflux (dich); DMS; pH<4; Complications - 6 months	25
Fibbe (Strate et al., 2008; Zornig et al., 2002)	Germany	Nissen (SGVD, B) vs. PPF	Dysphagia (dich); Reflux (dich); Reoperations - 4 months and 2 years DMS; Dilatations - 4 months	200
Gear (Eyre-Brook et al., 1993; Gear et al., 1984)	UK	Nissen (SGVD, B) vs. Angelchik	Reoperations; GBS (dich); Complications - 1 and 3 years Dysphagia (dich); Reflux (dich) - 1 year	52

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Granderath et al., 2005)	Austria	Nissen (SGVD, NS) vs. Nissen with mesh hiatoplasty	Dysphagia (dich); Reflux (dich); DMS - 1 year	100
(Granderath et al., 2007)	Austria	Nissen (SGVD, NS) vs. PPF	Dysphagia (dich); Reflux (dich); DMS; GBS (cont and dich); Complications - 3 months	56
(Guerin et al., 2007)	Belgium	Nissen (SGVP, B) vs. PPF	Dysphagia (dich); Reflux (dich); Complications - 1 and 3 years	140
(Engstrom et al., 2007; Hagedorn et al., 2003)	Sweden	PPF vs. APF	Dysphagia (dich); Reflux (dich); Reoperations - 1 and >5 years pH<4 - 1 year	95
(Khan et al., 2009)	UK	Nissen (SGVP, B) vs. PPF	Dysphagia (cont and dich); Reflux (dich); pH<4; Reoperations; Complications - 1 year	121
(Khan et al., 2010)	UK	PPF vs. APF	Dysphagia (cont and dich); Reflux (dich); pH<4; Reoperations; Complications - 1 year	103

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Kmiot et al., 1991)	UK	Nissen (SGVD, B) vs. Angelchik	Dysphagia (dich); Reflux (dich); GBS (dich); Complications - 2 years pH<4; Reoperations - 1 year	50
(Koch et al., 2013)	Austria	Nissen (NS) vs. PPF	GQOL; Dysphagia (cont); Reflux (cont); DMS; GBS (cont); Reoperations - 1 year	125
(Kosek et al., 2009)	Austria	Nissen (SGVP, B) vs. Nissen (SGVD, B)	Dysphagia (dich); Reflux (dich); Dilatations - 6 months and 5 years GQOL; DMS - 5 years	41
(Laws et al., 1997)	USA	Nissen (SGVD, B) vs. PPF	Dysphagia (dich); Dilatations; Complications - 2 years	39
LOTUS (Galmiche et al., 2011; Hatlebakk et al., 2016)	Sweden	Nissen (SGVD, B) vs. PPI	pH<4 - 6 months and >5 years GQOL; Dysphagia (dich); Reflux (cont and dich) - 6 months and 3 years	554

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
Lundell (Hagedorn et al., 2002; Lundell et al., 1996; Lundell et al., 1991; Rydberg et al., 1999)	Sweden	Nissen (SGVD, NB) vs. PPF	Dysphagia (dich); Reflux (dich); Complications - 1, 3 and 12 years pH<4 - 1 and 3 years Reoperations - 3 and 12 years	137
(Luostarinen et al., 1995; Luostarinen and Isolauri, 1999; Luostarinen et al., 1996)	Finland	Nissen (SGVP, B) vs. Nissen (SGVD, B)	Dysphagia (dich); Reflux (dich); Dilatations - 6 months and 3 years	50
(Mahon et al., 2005; Mehta et al., 2006)	UK	Nissen (SGVP, NS) vs. PPI	DMS; pH<4; Dilatations; Reoperations; Complications - 1 year	217

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Mickevicius et al., 2008; Mickevicius et al., 2013)	Lithuania	Nissen (SGVD, B) vs. PPF	Dysphagia (dich); Reflux (dich); Dilatations; GBS (dich); Complications - 1 and 5 years DMS - 1 year	153
(Mucio et al., 2012)	Mexico	Nissen (SGVD, B) vs. PPF vs. FND 360º§	Reoperations; Complications - 15 years QOL - 10 years Dysphagia (dich) - 1 year	385
(Muller-Stich et al., 2015)	Germany, Switzerland	Nissen (SGVD, B) vs. Mesh hiatoplasty with cardiophrenicopexy	GQOL; Dysphagia (cont); Reflux (cont); GBS (cont); Complications - 1 and 3 years Dilatations; Reoperations - 3 years DMS - 1 year	90
(Patterson et al., 2000)	USA	Nissen (SGVD, B) vs. Nissen (SGVD, NB)	Dysphagia (cont and dich); Dilatations - 6 months	171
(Qin et al., 2013)	China	Nissen (NS) vs. PPF	Reflux (dich) - 5 years Dysphagia (dich); DMS - 3 months	383

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Raue et al., 2011)	Germany	Nissen (SGVD, B) vs. APF	GQOL; DMS; Dilatations; Reoperations; Complications - 18 months	64
(Roks et al., 2017b)	Netherlands	PPF vs. APF	Dysphagia (cont and dich); Reflux (cont and dich); pH<4; Reoperations; GBS (dich); Complications - 1 year	94
(Segol et al., 1989)	France	Nissen (SGVP, B) vs. PPF vs. 90º¶	Dysphagia (dich); Reflux (dich); DMS; Reoperations; Complications - 2 years	47
(Shaw et al., 2010)	South Africa	Nissen (SGVD, B) vs. PPF	Dysphagia (cont); Reflux (cont); GBS (cont) - 3 months and 5 years Reoperations - 5 years DMS; pH<4 - 3 months	100
Stuart (Hill et al., 1994; Stuart et al., 1989)	Ireland	Nissen (SGVP, NS) vs. Angelchik	Dysphagia (dich); Complications - 3 and 7 years pH<4 - 1 and 7 years Dilatations - 7 years GBS (dich) - 3 years	61

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
(Thor and Silander, 1989)	Sweden	Nissen (SGVD, B) vs. PPF	Dysphagia (dich); Complications - 5 years	31
Walker (Baxter et al., 1996; Walker et al., 1992)	UK	Nissen (NS, B) vs. PPF	pH<4; Complications - 13 months and 10 years Dysphagia (dich); Reflux (dich); Dilatations; GBS (dich) - 13 months	52
(Wang et al., 2015)	China	Nissen (SGVD, NB) vs. PPF	Dysphagia (dich); Reflux (dich); DMS; Complications - 4 years	84
(Washer et al., 1984)	UK	Nissen (NS) vs. REY duodenal diversion	Dilatations; Reoperations; Complications - 5 years	44
Watson 1997 (O'Boyle et al., 2002; Watson et al., 1997; Yang et al., 2008)	Australia	Nissen (SGVD, B) vs. Nissen (SGVP, B)	Dysphagia (cont and dich); Reflux (cont and dich); Reoperations; Complications - 6 months, 5 and 10 years Dilatations - 5 years pH<4 - 3 months	102

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
Watson 1999 (Cai et al., 2008; Ludemann et al., 2005; Watson et al., 1999)	Australia	Nissen (SGVP, B) vs. APF	Dysphagia (cont and dich); Reflux (cont and dich); Reoperations; Complications - 6 months, 5 and 10 years Dilatations - 6 months	107
Watson 2004 (Nijjar et al., 2010; Watson et al., 2004; Woodcock et al., 2006)	Australia, NZ	Nissen (SGVD, B) vs. 90^{o}	QOL; Dysphagia (cont and dich); Reflux (cont and dich); Reoperations; Complications - 1 and 5 years pH<4 - 3 months	112
Watson 2012 (Spence et al., 2006; Watson et al., 2012)	Australia	Nissen (SGVP, B) vs. 90^{o}	Dysphagia (cont and dich); Reflux (cont and dich); Reoperations; Complications - 1 and 5 years pH<4 - 6 months	79

Table 3.2 continued

Trial references	Country	Interventions	Reported outcomes* - and time points†	Patients‡
Watson 2013 (Daud et al., 2015)	Australia	PPF vs. APF	Dysphagia (cont and dich); Reflux (cont and dich); Complications - 1 year pH<4 - 6 months	47
(Yigit et al., 2012)	Turkey	Nissen (NS) vs. Nissen with fascial graft	Dysphagia (dich) - 7 months	24

*Outcomes relevant to this review. †Follow-up time points at which trial data for eligible outcomes were reported and used in this review (except for postoperative complications, which were not split in this review by follow-up time point). Some trials reported data for more than one time point within this review's pre-specified follow-up periods, in such instances the latter time point was used. Where a specific figure was not reported by the trial investigators, the mean follow-up time was used. ‡Total number of patients randomised in the trial, or number analysed if total number randomised not reported. The number of patients for whom data were reported for different outcomes at different time points varied. §Trial report also included a fourth observational PPI arm, which was excluded as not randomised. ¶This arm in the trial underwent a Lortat-Jacob procedure, which is the same in principle and technique as a 90 degree fundoplication.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. B = Bougie. Cont = Continuous data (scores). Dich = Dichotomous data (rates). DMS = DeMeester score (oesophageal acid exposure). FND 360º = Fixed 'non-deformable' 360 degree fundoplication. GBS = Gas bloat syndrome. GQOL = Gastrointestinal, or reflux disease specific quality of life score. NB = No bougie. NS = Short gastric vessel division and/or use of bougie use (in Nissen) not specified in methods, or left up to the individual surgeon with no further information available. pH<4 = Total oesophageal acid exposure time (percentage time pH < 4). PPI = Proton pump inhibitor therapy. PPF = Posterior partial fundoplication. QOL = Quality of life score. REY = Roux-en-Y. SGVD = Short gastric vessel division. SGVP = Short gastric vessel preservation.

Table 3.3 Data available for each outcome follow-up time point

Outcome	3-12 months		>1-5 years		>5-10 years		>10 years	
	Trials	**Patients**	**Trials**	**Patients**	**Trials**	**Patients**	**Trials**	**Patients**
Health-related QOL	3	259	2	205	2	284	0	0
Gastrointestinal/reflux specific QOL	4	706	3	478	0	0	0	0
Dysphagia rate	22	2708	16	1717	2	136	2	200
Dysphagia scores	16	1436	7	686	4	327	1	85
Reflux rate	20	1961	13	1806	3	273	1	110
Reflux scores	13	1565	8	1045	3	246	1	90
Oesophageal acid exposure scores	11	1283	4	280	1	96	0	0
Total oesophageal acid exposure time	17	1430	4	280	4	336	0	0
Dilatation for dysphagia rate	8	940	7	688	1	47	0	0
Reoperation rate	14	1513	13	1309	3	273	3	432
Gas bloat rate	5	360	5	333	0	0	1	90
Gas bloat scores	4	349	2	155	0	0	0	0

Postoperative complications are not included in this table as this outcome was not split by follow-up time point. Postoperative complications were reported by 31 trials, with data available for 2688 patients.

QOL = Quality of life score.

Figure 3.2 summarises the risk of bias assessment of the included trials, and Figure 3.3 shows the domain assessment for individual trials, categorised by comparison. Only seven trials were judged at low risk of bias across all domains. Many trials did not provide details on blinding and allocation concealment, although over a quarter were judged as well-blinded.

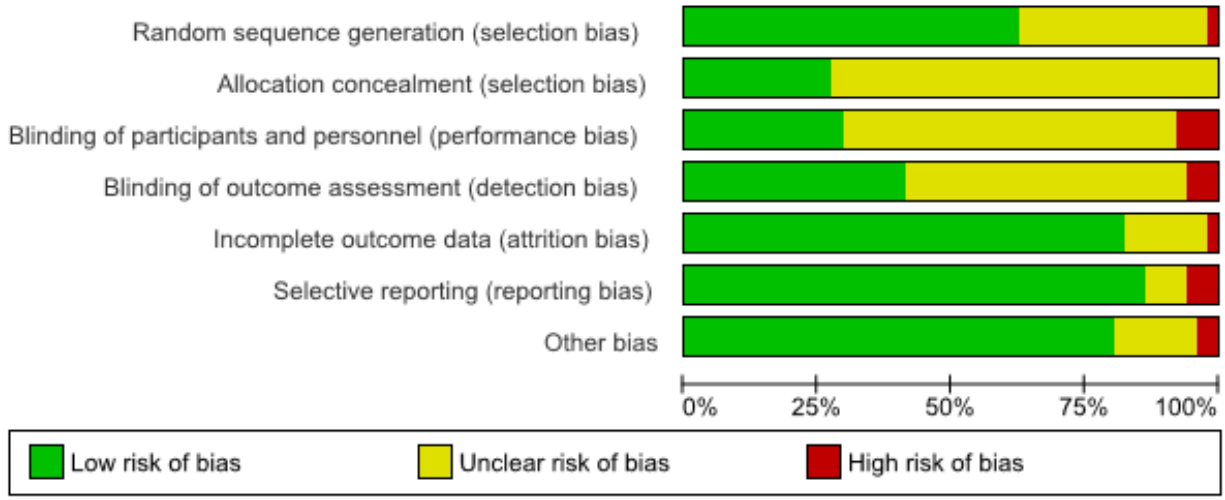


Figure 3.2 Risk of bias assessment summary figure

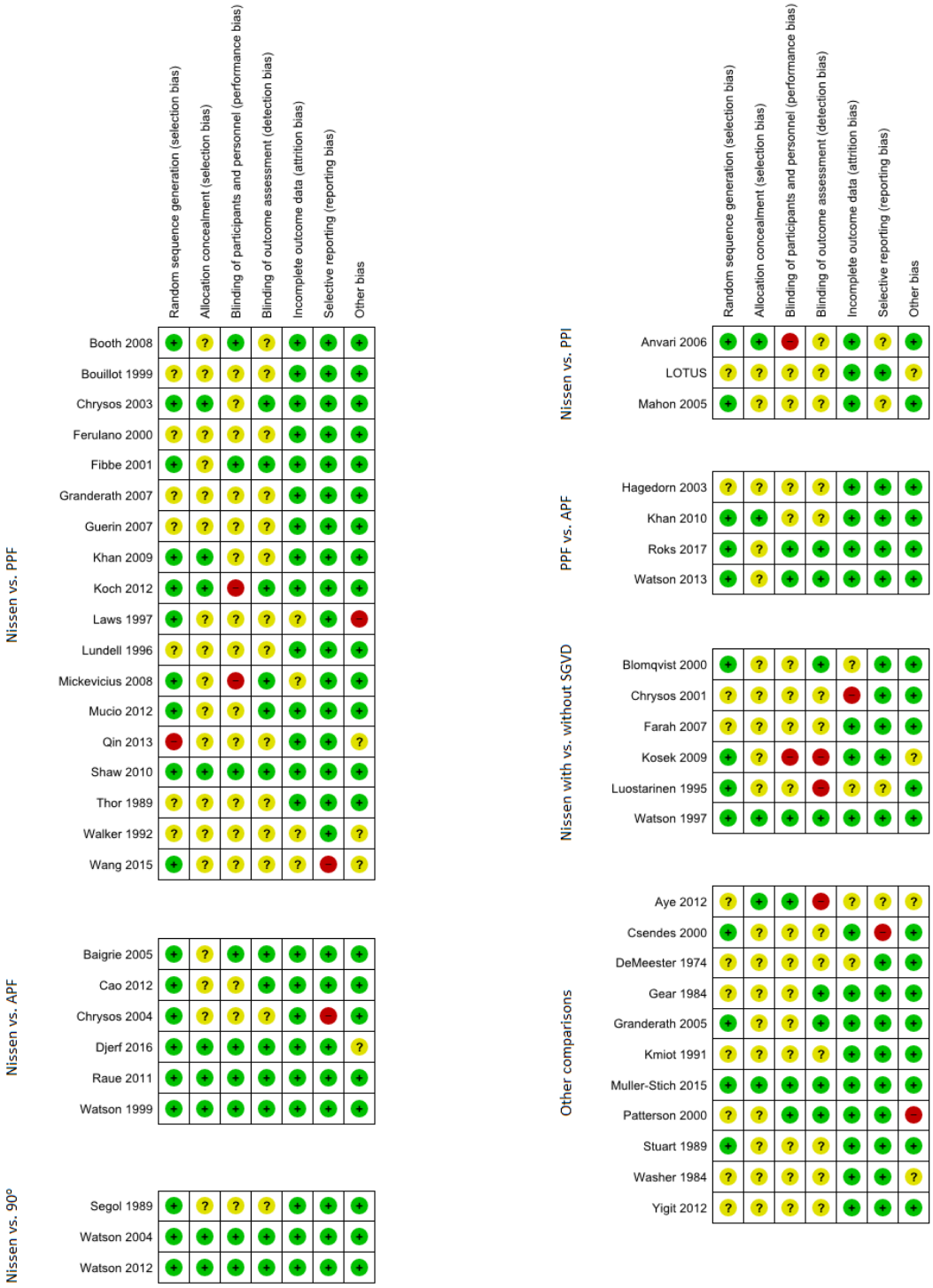


Figure 3.3 Risk of bias assessment by individual study

+ denotes low risk; ? denotes unclear risk; − denotes high risk of bias, for each given domain, as judged by the authors. Sorted by comparison.

90° = 90 degree fundoplication. APF = Anterior partial fundoplication. PPI = Proton pump inhibitor therapy. PPF = Posterior partial fundoplication. SGVD = Short gastric vessel division.

3.4.2 Quality of life scores

Both general (health-related) and gastrointestinal/reflux specific QOL 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 3.3). This paucity of data led to a decision, prior to analysis, to add reflux as a primary outcome, to facilitate its use as the main measure of efficacy in this review.

Figures 3.4 and 3.5 summarise the direct evidence available for these outcomes at 3-12 months, and Tables 3.4 and 3.5 report the NMA results. In general, patients who underwent surgery had significantly better QOL scores than those on PPI therapy, and those who underwent an APF or PPF had better general QOL scores than those who underwent a Nissen fundoplication, though this was not always statistically significant across all time points. Pairwise meta-analysis and all sensitivity analyses showed similar findings to the main analysis. There were not enough data to statistically test for heterogeneity or inconsistency.

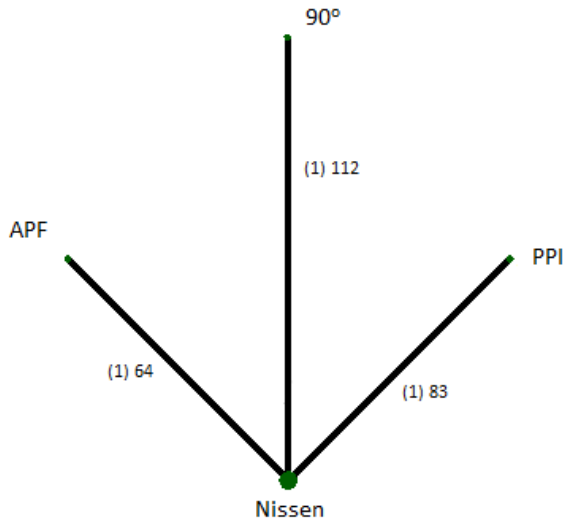


Figure 3.4 Network map of direct evidence for health-related quality of life scores

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPI = Proton pump inhibitor.

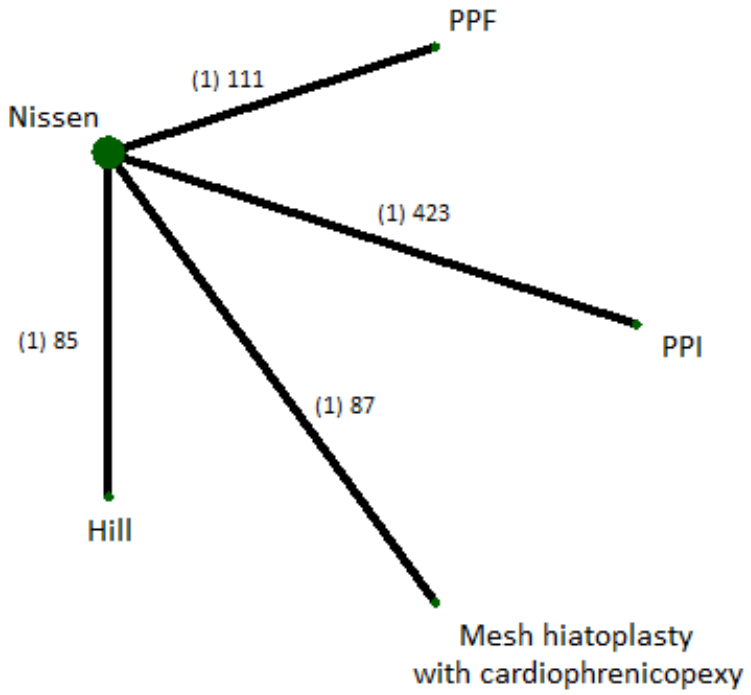


Figure 3.5 Network map of direct evidence for gastrointestinal/reflux specific quality of life scores

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.4 Network meta-analysis results – Health-related quality of life scores

3-12 months			
	90º	**APF**	**Nissen**
PPI	1.71 (1.11, 2.31)*	0.79 (0.13, 1.46)*	0.38 (-0.05, 0.82)
90º		-0.92 (-1.56,- 0.27)*	-1.33 (-1.74, -0.92)*
APF			-0.41 (-0.91, 0.08)
1-5 years			
	90º	**Nissen**	
PPI	0.28 (-0.28, 0.83)	0.34 (-0.07, 0.75)	
90º		0.06 (-0.31, 0.43)	
5-10 years			
	PPF	**Nissen**	
APF	-0.32 (-0.90, 0.25)	0.15 (-0.35, 0.66)	
PPF		0.47 (0.21, 0.74)*	

*P < 0.05. Values in parentheses are 95% confidence intervals. Standardised mean difference, expressed as standard deviations. A positive value indicates that patients who underwent the treatment in the corresponding cell in the top row had better quality of life scores than patients who underwent the treatment in the corresponding cell in the left hand column, and a negative value indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.5 Network meta-analysis results – Gastrointestinal/reflux specific quality of life scores

3-12 months				
	PPF	**Nissen**	**Hill**	**MHWC**
PPI	0.84 (0.41, 1.27)*	0.56 (0.35, 0.76)*	0.56 (0.07, 1.04)*	0.50 (0.03, 0.97)*
PPF		-0.29 (-0.67, 0.09)	-0.29 (-0.87, 0.29)	-0.34 (-0.92, 0.23)
Nissen			0.00 (-0.44, 0.44)	-0.06 (-0.48, 0.37)
Hill				-0.06 (-0.67, 0.55)
1-5 years				
	APF	**Nissen**	**MHWC**	
PPI	0.39 (-0.18, 0.96)	0.47 (0.25, 0.70)*	0.52 (0.03, 1.01)*	
APF		0.08 (-0.44, 0.61)	0.13 (-0.56, 0.81)	
Nissen			0.04 (-0.39, 0.48)	

*P < 0.05. Values in parentheses are 95% confidence intervals. Standardised mean difference, expressed as standard deviations. A positive value indicates that patients who underwent the treatment in the corresponding cell in the top row had better quality of life scores than patients who underwent the treatment in the corresponding cell in the left hand column, and a negative value indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.

90^{o} = 90 degree fundoplication. APF = Anterior partial fundoplication. MHWC = Mesh hiatoplasty with cardiophrenicopexy. PPI = Proton pump inhibitor.

3.4.3 Reflux

Reflux was the most commonly reported efficacy outcome (Table 3.3). Figures 3.6 and 3.7 summarise the direct evidence available at 3-12 months, for rates and scores respectively.

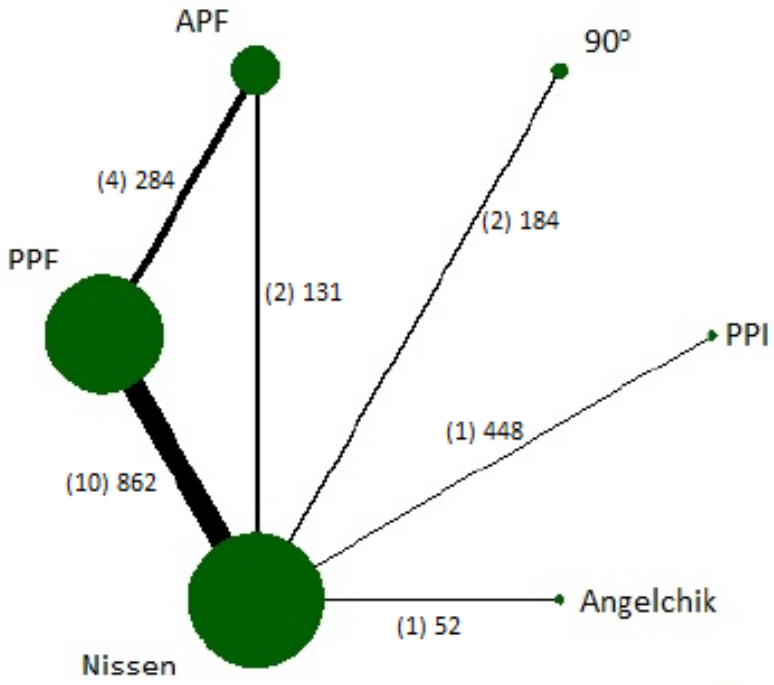


Figure 3.6 Network map of direct evidence for reflux rate

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90° = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

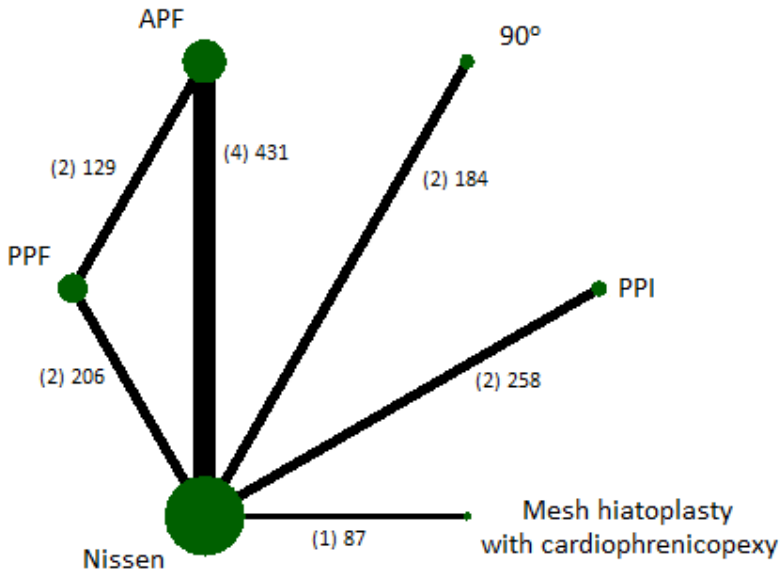


Figure 3.7 Network map of direct evidence for reflux scores

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Tables 3.6 (rate data) and 3.7 (score data) report reflux NMA results. 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.

Table 3.6 Network meta-analysis results – Reflux rate

3-12 months					
	90º	**APF**	**PPF**	**Nissen**	**Angelchik**
PPI	0.69 (0.17, 2.85)	0.79 (0.22, 2.81)	0.47 (0.15, 1.45)	0.34 (0.13, 0.92)*	0.02 (0.00, 0.50)*
90º		1.14 (0.31, 4.20)	0.68 (0.21, 2.18)	0.50 (0.18, 1.38)	0.03 (0.00, 0.74)*
APF			0.59 (0.30, 1.19)	0.43 (0.19, 0.97)*	0.03 (0.00, 0.60)*
PPF				0.73 (0.42, 1.27)	0.04 (0.00, 0.96)*
Nissen					0.06 (0.00, 1.26)
1-5 years					
	90º	**APF**	**PPF**	**Nissen**	**Angelchik**
PPI	0.72 (0.12, 4.46)	1.08 (0.11, 10.75)	0.47 (0.09, 2.49)	0.47 (0.11, 2.07)	0.98 (0.04, 23.32)
90º		1.50 (0.19, 11.63)	0.66 (0.20, 2.14)	0.65 (0.23, 1.88)	1.36 (0.07, 27.13)
APF			0.44 (0.07, 2.94)	0.43 (0.08, 2.51)	0.91 (0.03, 24.65)
PPF				0.99 (0.47, 2.10)	2.08 (0.11, 37.58)
Nissen					2.09 (0.13, 34.26)
5-10 years					
	PPF	**Nissen**			
APF	0.21 (0.08, 0.53)*	0.87 (0.40, 1.88)			
PPF		4.10 (1.24, 13.56)*			

*P < 0.05. Values in parentheses are 95% confidence intervals. Unit is odds ratio. A value >1 indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher reflux rate than patients who underwent the treatment in the corresponding cell in the left hand column, and a value <1 indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.7 Network meta-analysis results – Reflux scores

3-12 months					
	90º	**APF**	**PPF**	**Nissen**	**MHWC**
PPI	-0.51 (-0.93, -0.10)*	-0.59 (-0.91, -0.26)*	-0.72 (-1.09, -0.36)*	-0.74 (-0.99, -0.48)*	-0.17 (-0.71, 0.37)
90º		-0.07 (-0.46, 0.31)	-0.21 (-0.62, 0.20)	-0.22 (-0.55, 0.10)	0.35 (-0.23, 0.92)
APF			0.35 (-0.23, 0.92)	-0.13 (-0.40, 0.13)	-0.15 (-0.35, 0.05)
PPF				-0.01 (-0.27, 0.24)	0.55 (0.01, 1.09)*
Nissen					0.57 (0.09, 1.04)*
1-5 years					
	90º	**APF**	**PPF**	**Nissen**	**MHWC**
PPI	-0.30 (-0.87, 0.27)	-0.51 (-1.01, -0.01)*	-0.95 (-1.67, -0.24)*	-0.57 (-0.98, -0.16)*	0.09 (-0.61, 0.79)
90º		-0.21 (-0.70, 0.28)	-0.66 (-1.36, 0.05)	-0.28 (-0.67, 0.12)	0.39 (-0.30, 1.08)
APF			-0.45 (-1.10, 0.20)	-0.06 (-0.36, 0.23)	0.60 (-0.04, 1.24)
PPF				0.38 (-0.20, 0.96)	1.05 (0.23, 1.86)*
Nissen					0.67 (0.10, 1.23)
5-10 years					
	Nissen				
APF	-0.41 (-0.82, 0.01)				

*P < 0.05. Values in parentheses are 95% confidence intervals. Standardised mean difference, expressed as standard deviations. A positive value indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher reflux score (more reflux) than patients who underwent the treatment in the corresponding cell in the left hand column, and a negative value indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. MHWC = Mesh hiatoplasty with cardiophrenicopexy. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

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 similarly low reflux rates as Angelchik. Fundoplication rankings for reflux rate are shown in Figure 3.8, with NF and PPF ranking as the best treatments, followed by the other fundoplications and PPI respectively. Sensitivity analysis splitting the Nissen node into four groups (according to bougie use and short gastric division/preservation) showed no significant difference between Nissen fundoplication and APF. Sensitivity analysis reallocating 120º anterior partial fundoplications to 90º resulted in a statistically significant decrease in the rate of reflux with PPF in comparison with PPI or 90º, as well as the difference between Nissen and 90º becoming statistically significant. The difference between APF and Nissen was no longer statistically significant, but overall network rankings remained unchanged.

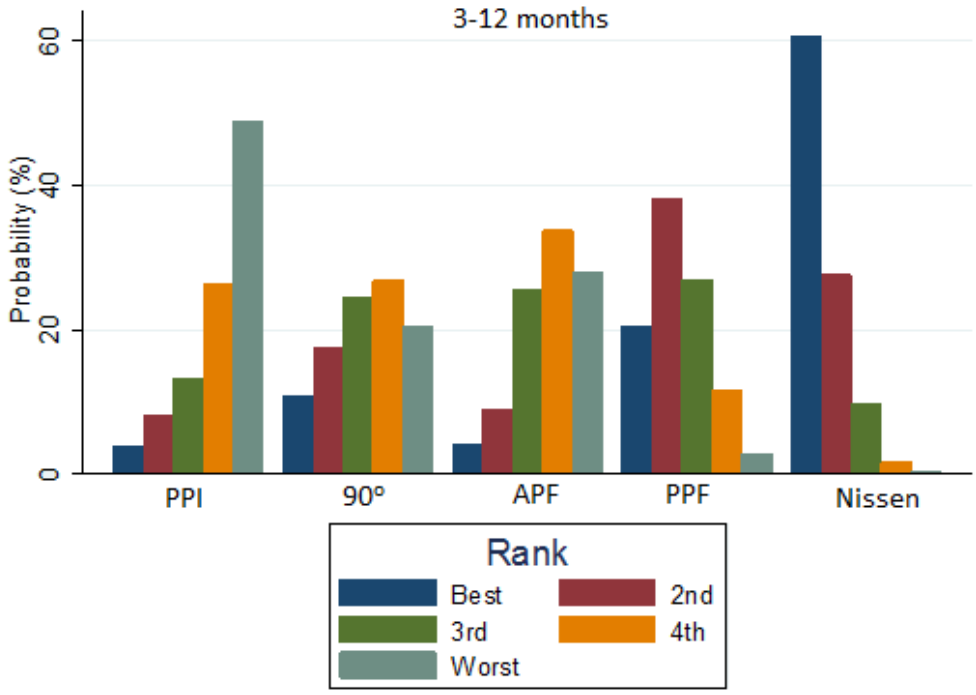


Figure 3.8 Rankogram of fundoplications according to reflux rate

The probability of each included fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is represented by the coloured bars. There were no significant differences at 1-5 years, and insufficient data for ranking at 5-10 years, so rankograms for those time points are not shown.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Analysis of score data at 3-12 months showed that all fundoplications had significantly lower reflux scores compared to PPI therapy, but there were no significant differences between the fundoplications. Sensitivity analysis splitting the Nissen node into four groups resulted in the difference between PPI and all partial fundoplications except PPF to become no longer statistically significant. Both NF and PPF had significantly lower reflux scores than mesh hiatoplasty with cardiophrenicopexy (MHWC). Figure 3.9 shows the fundoplication rankogram for reflux scores, with similar rankings to reflux rate.

At 1-5 year follow-up, there were no significant differences between the groups in the main analysis of rate data. Sensitivity analysis splitting the Nissen node into four groups (according to bougie use and short gastric division/preservation) revealed a significant reduction in the rate of reflux with PPF in comparison with PPI and APF, with no other significant differences between the treatments. Score data analysis showed a significant reduction in reflux scores with any fundoplication in comparison with PPI, except 90^{o}. PPF alone showed significantly lower reflux scores compared to MHWC. Sensitivity analysis splitting the Nissen node into four groups resulted in the difference between APF and PPI to become no longer statistically significant. The fundoplication rankogram for score data is shown in Figure 3.9, with PPF ranking as the best treatment.

At long-term follow-up, PPF patients were significantly less likely to report reflux symptoms than APF or NF patients, though this was based on rate data from only three studies. Score data were only available for APF and NF, with no significant difference found. One study reported data at >10 years follow-up, with no significant difference in reflux rates shown between NF and PPF.

Apart from the 5-10 year comparisons where predictive intervals were wide (suggesting significant between-study heterogeneity), there was no evidence of significant inconsistency or heterogeneity in the analyses for this outcome.

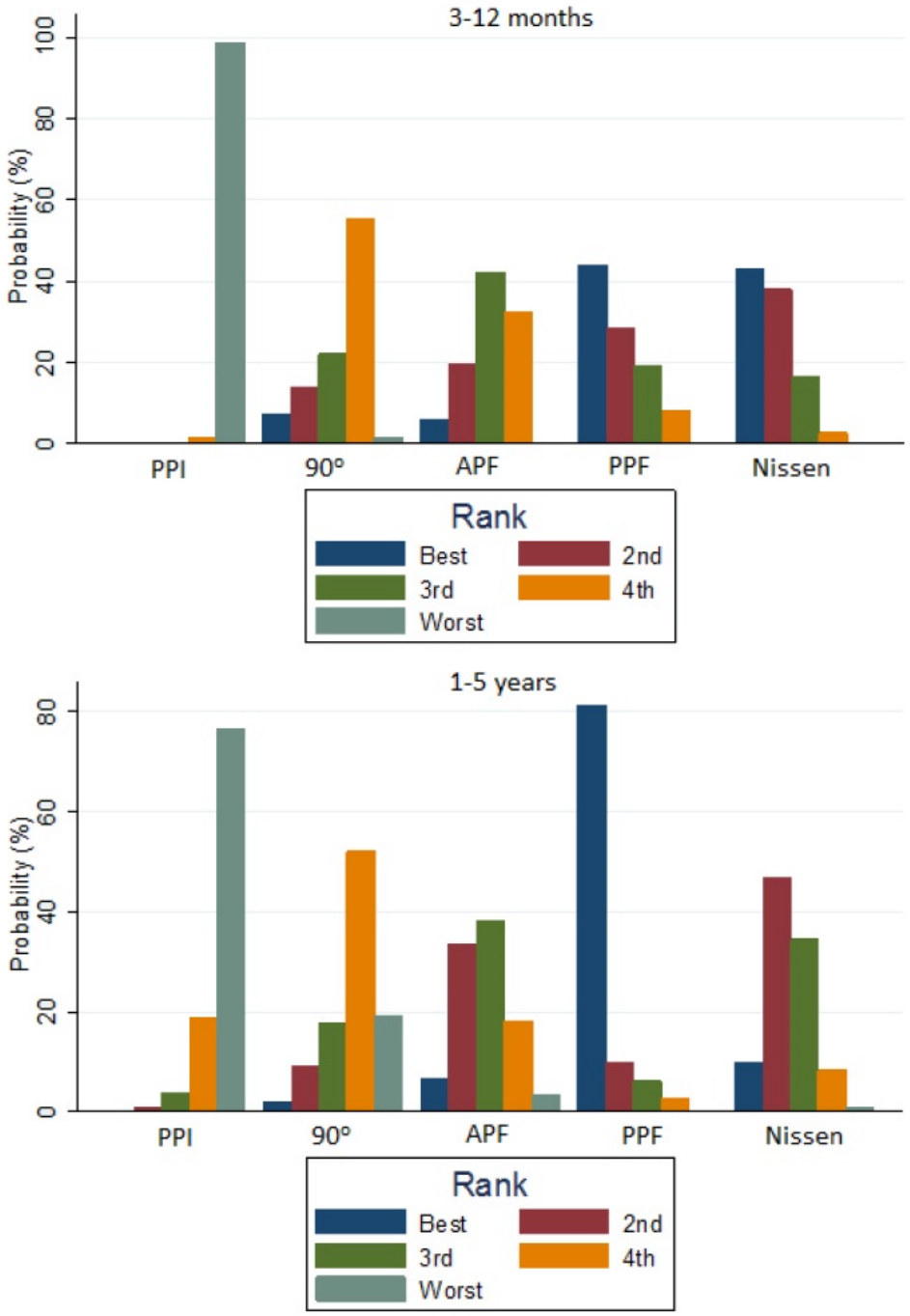


Figure 3.9 Rankogram of fundoplications according to reflux scores

The probability of each included fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is represented by the coloured bars, at each time point. Missing time points mean insufficient data available at that time point for ranking.

90° = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

3.4.4 Dysphagia

A large number of trials reported this outcome (Table 3.3). Figures 3.10 and 3.11 summarise the direct evidence available at 3-12 months, for rates and scores respectively.

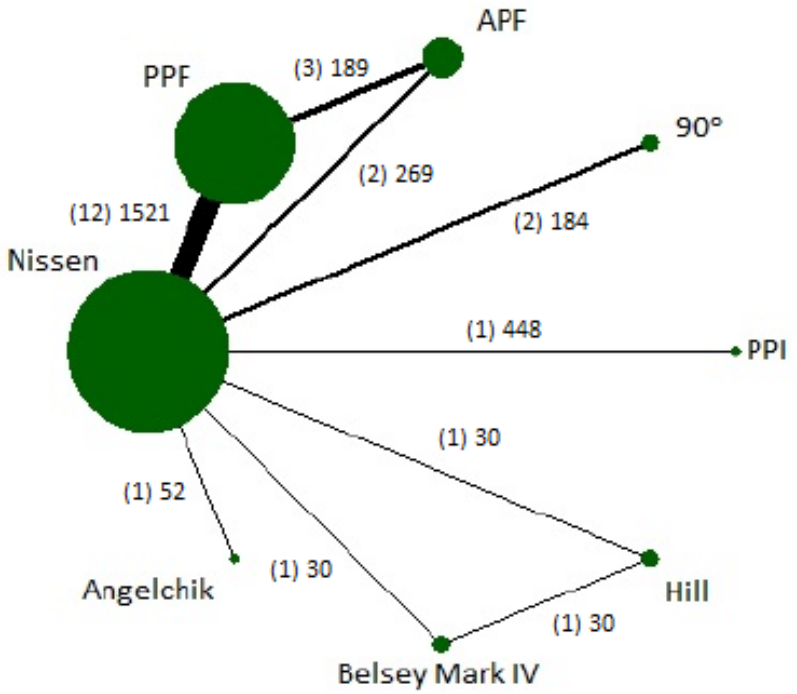


Figure 3.10 Network map of direct evidence for dysphagia rate

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

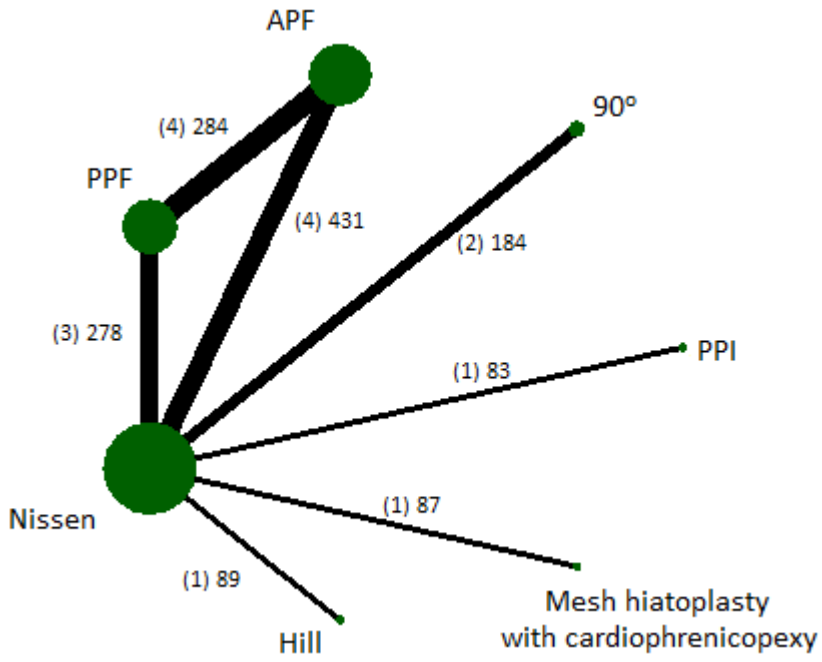


Figure 3.11 Network map of direct evidence for dysphagia scores

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90^{o} = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Tables 3.8 (rate data) and 3.9 (score data) report NMA results. Both showed similar overall findings and rankings across all time points, despite some variation in the treatment effect point estimates and confidence intervals.

Table 3.8 Network meta-analysis results – Dysphagia rate

3-12 months							
	90º	**APF**	**PPF**	**Nissen**	**Angelchik**	**BM IV**	**Hill**
PPI	1.19 (0.39, 3.62)	2.13 (0.78, 5.86)	2.15 (0.82, 5.64)	5.51 (2.24, 13.55)*	18.94 (3.81, 94.06)*	0.57 (0.07, 4.27)	5.51 (0.56, 54.38)
90º		1.79 (0.80, 4.00)	1.81 (0.86, 3.80)	4.63 (2.40, 8.93)*	15.93 (3.63, 69.96)*	0.48 (0.07, 3.27)	4.63 (0.51, 42.05)
APF			1.01 (0.61, 1.66)	2.58 (1.63, 4.10)*	8.89 (2.18, 36.19)*	0.27 (0.04, 1.72)	2.58 (0.30, 22.31)
PPF				2.56 (1.81, 3.62)*	8.80 (2.24, 34.66)*	0.26 (0.04, 1.66)	2.56 (0.30, 21.62)
Nissen					3.44 (0.91, 12.95)	0.10 (0.02, 0.63)*	1.00 (0.12, 8.21)
Angelchik						0.03 (0.00, 0.28)*	0.29 (0.02, 3.50)
BM IV							9.75 (1.59, 59.69)*
1-5 years							
	90º	**APF**	**PPF**	**Nissen**	**Angelchik**		
PPI	1.24 (0.26, 5.85)	1.03 (0.21, 5.16)	1.34 (0.32, 5.69)	3.29 (0.91, 11.81)	29.16 (2.96, 285.95)*		
90º		0.84 (0.22, 3.12)	1.09 (0.36, 3.27)	2.66 (1.10, 6.44)*	23.60 (2.91, 191.31)*		
APF			1.30 (0.40, 4.27)	3.19 (1.20, 8.48)*	28.26 (3.34, 238.92)*		
PPF				2.44 (1.25, 4.77)*	21.70 (2.91, 161.85)*		
Nissen					8.87 (1.33, 59.07)*		
5-10 years							
	Nissen	**Angelchik**					
APF	2.10 (0.89, 4.95)	14.78 (1.35, 162.02)*					
Nissen		7.05 (0.75, 65.92)					

Table 3.8 continued

>10 years		
	PPF	**Nissen**
APF	0.87 (0.20, 3.71)	0.83 (0.25, 2.70)
PPF		0.96 (0.41, 2.24)

*P < 0.05. Values in parentheses are 95% confidence intervals. Unit is odds ratio. A value >1 indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher dysphagia rate than patients who underwent the treatment in the corresponding cell in the left hand column, and a value <1 indicates the opposite. Missing treatments mean no data available at this follow-up time point.

90^{o} = 90 degree fundoplication. BM IV = Belsey Mark IV. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.9 Network meta-analysis results – Dysphagia scores

3-12 months						
	90º	**APF**	**PPF**	**Nissen**	**Hill**	**MHWC**
PPI	0.63 (-0.43, 1.70)	0.29 (-0.65, 1.23)	0.17 (-0.78, 1.13)	-0.15 (-1.02, 0.72)	0.00 (-1.23, 1.23)	-0.15 (-1.37, 1.08)
90º		-0.34 (-1.06, 0.37)	-0.46 (-1.19, 0.27)	-0.78 (-1.40, -0.16)*	-0.63 (-1.70, 0.43)	-0.78 (-1.84, 0.28)
APF			-0.12 (-0.49, 0.25)	-0.44 (-0.80, -0.07)*	-0.29 (-1.23, 0.65)	-0.44 (-1.38, 0.50)
PPF				-0.32 (-0.71, 0.07)	-0.17 (-1.12, 0.78)	-0.32 (-1.27, 0.63)
Nissen					0.15 (-0.72, 1.01)	0.00 (-0.87, 0.87)
Hill						-0.15 (-1.37, 1.08)
1-5 years						
	APF	**PPF**	**Nissen**	**MHWC**		
90º	0.09 (-0.32, 0.50)	-0.03 (-0.64, 0.57)	-0.38 (-0.72, -0.04)*	-0.65 (-1.23, -0.07)*		
APF		-0.12 (-0.68, 0.43)	-0.47 (-0.70, -0.23)*	-0.74 (-1.27, -0.21)*		
PPF			-0.34 (-0.84, 0.16)	-0.61 (-1.30, 0.07)		
Nissen				-0.27 (-0.75, 0.20)		
5-10 years						
	PPF	**Nissen**				
APF	0.18 (-0.53, 0.89)	-0.71 (-1.14, -0.28)*				
PPF		-0.89 (-1.72, -0.06)*				

*P < 0.05. Values in parentheses are 95% confidence intervals. Standardised mean difference, expressed as standard deviations. A positive value indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher dysphagia assessment score (less dysphagia) than patients who underwent the treatment in the corresponding cell in the left hand column, and a negative value indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. MHWC = Mesh hiatoplasty with cardiophrenicopexy. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

At 3-12 month follow-up, NF patients had a significantly higher rate of dysphagia at 3-12 months than any other group apart from Angelchik and Hill repair. Sensitivity analysis reallocating 120^{o} anterior partial fundoplications to 90^{o} resulted in a statistically significant difference in dysphagia rates between PPF and 90^{o}. NF also had significantly higher dysphagia scores compared to APF or 90^{o} fundoplication. There were no significant differences between the partial fundoplications, or between any of them and PPI therapy. Sensitivity analysis by serial exclusion of individual PPF studies frequently resulted in the difference with Nissen at short-term follow-up to reach statistical significance. Fundoplication rankograms at short-term follow-up are shown in Figures 3.12 (rate data) and 3.13 (score data), with Nissen consistently ranking as the worst treatment, and PPF and APF ranking fairly similarly.

At 1-5 years, those who underwent any partial fundoplication were still significantly less likely to suffer from dysphagia, and have lower dysphagia scores, compared to those who received an NF. This is reflected in the fundoplication rankograms (Figures 3.12 and 3.13), with Nissen again ranking as the worst treatment.

At 5-10 year follow-up, NF still showed significantly higher dysphagia scores compared to APF or PPF. Rate data analysis showed similar point estimates, but with wider confidence intervals. One study reported >10 year score data for APF versus NF with no significant difference found.

Predictive intervals for all comparisons in this outcome were narrow, and inconsistency factors for all loops were small, suggesting no evidence of significant inconsistency or heterogeneity.

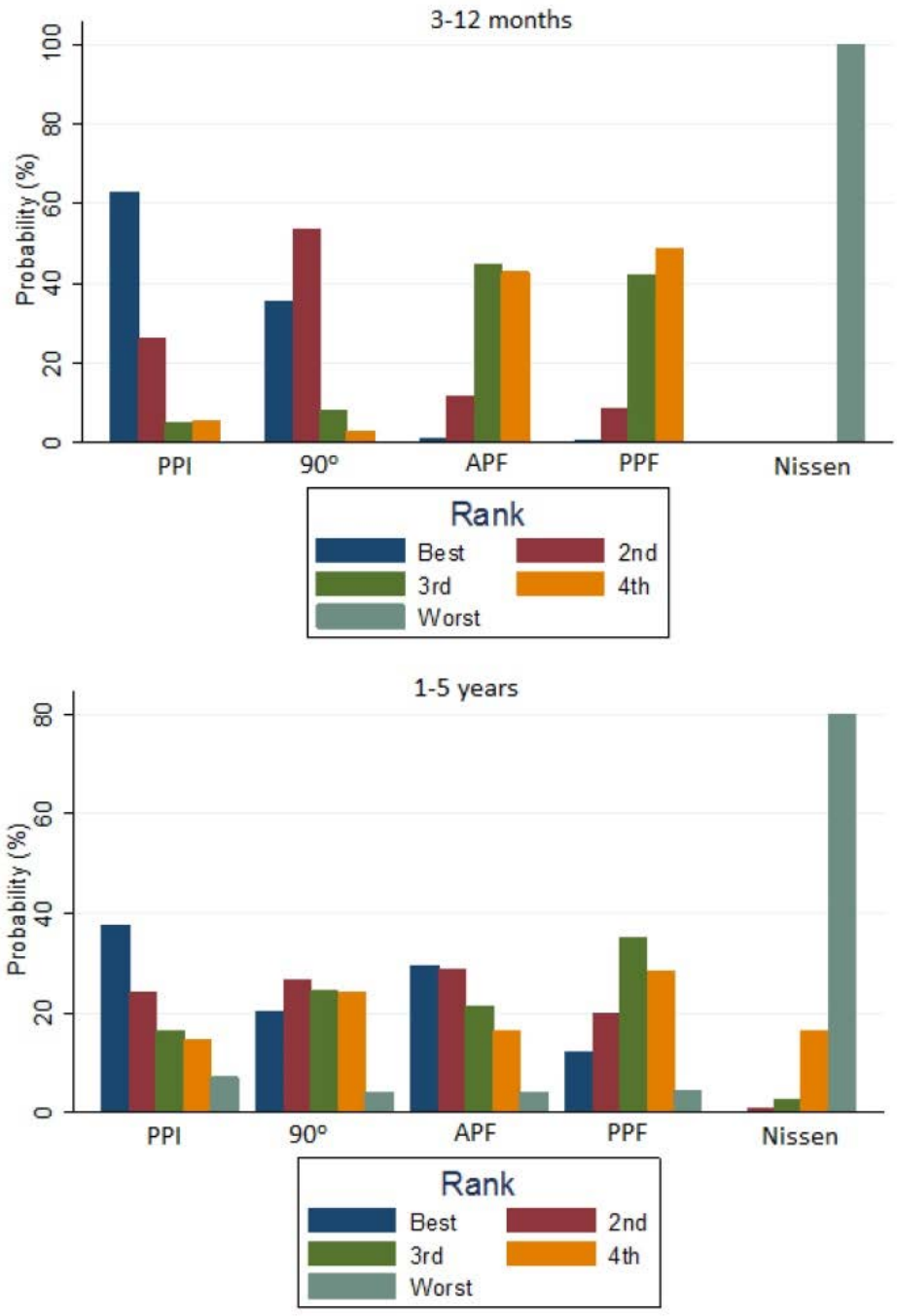


Figure 3.12 Rankogram of fundoplications according to dysphagia rate

The probability of each included fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is represented by the coloured bars, at each time point. Missing time points mean insufficient data available at that time point for ranking.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

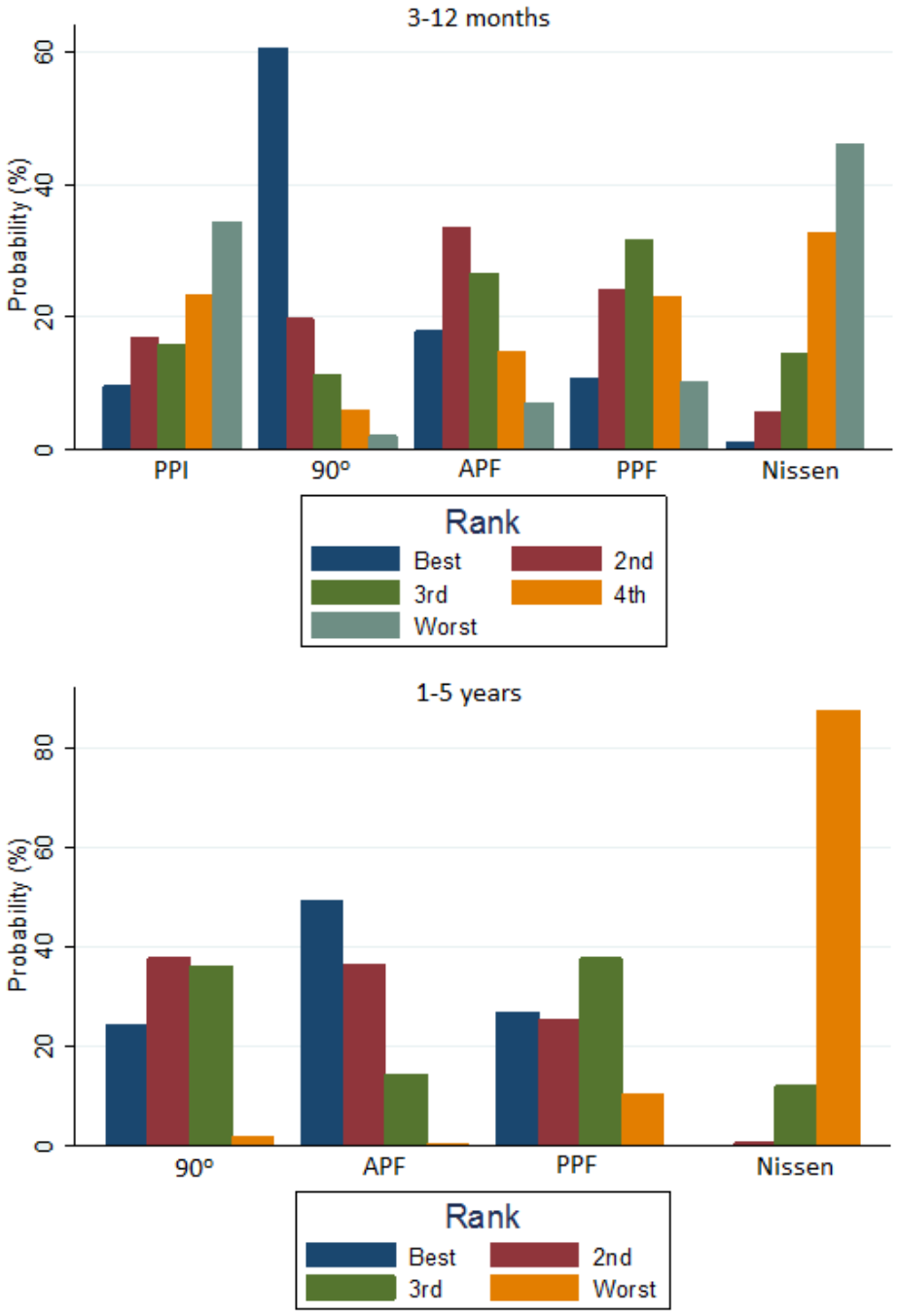


Figure 3.13 Rankogram of fundoplications according to dysphagia scores

The probability of each included fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is represented by the coloured bars, at each time point. Missing time points/treatments mean insufficient data available at that time point for ranking.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Comparison-adjusted funnel plots using reflux and dysphagia data for assessment of publication bias are shown in Figure 3.14. Study-specific effect sizes were evenly distributed around the pooled estimate line, with the exception of NF versus PPF studies reporting reflux rate data.

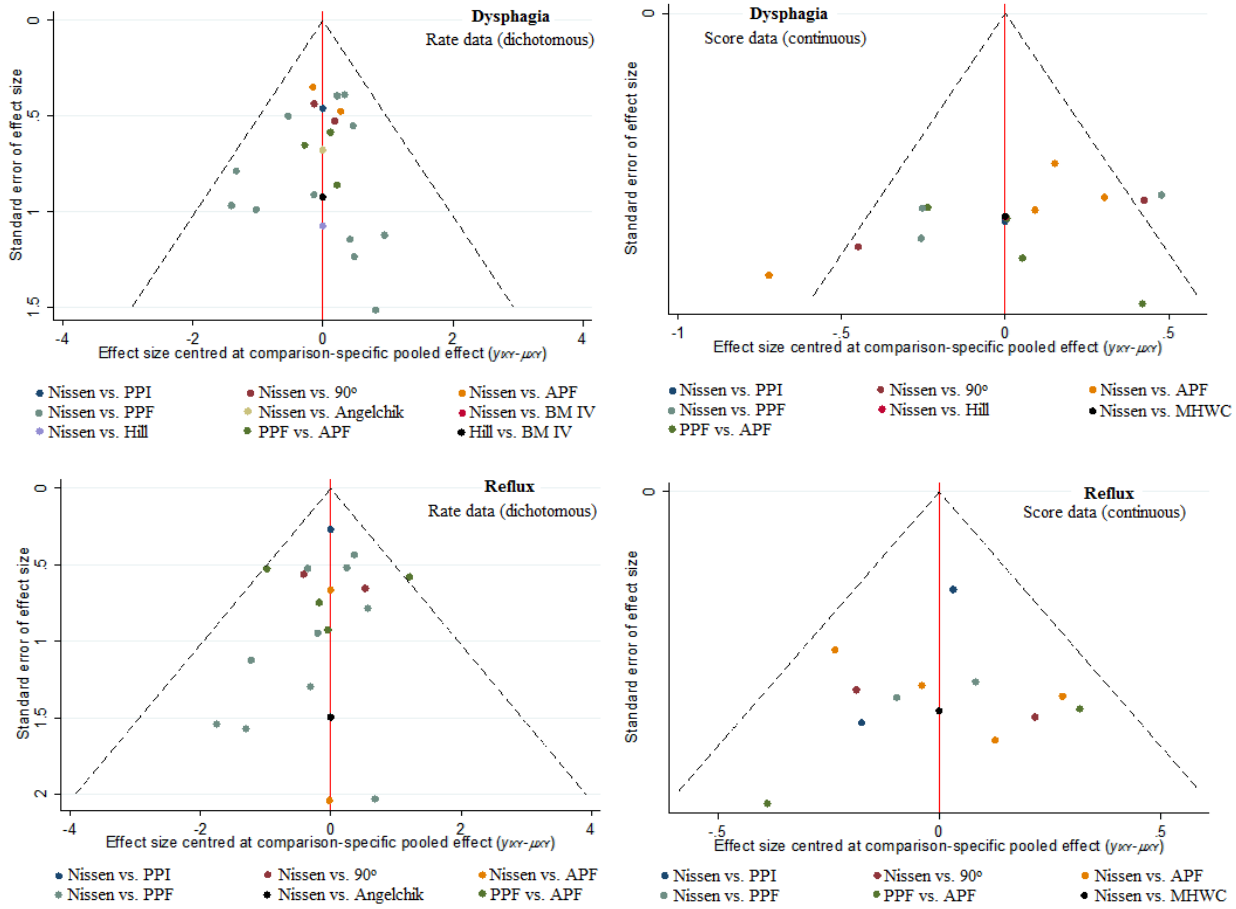


Figure 3.14 Comparison-adjusted funnel plots for dysphagia and reflux

3-12 month data. The zero line represents the null hypothesis that the study-specific effect sizes do not differ from the comparison-specific pooled estimates. Different coloured points on the plot represent the different comparisons, as in the key.

90° = 90 degree fundoplication. APF = Anterior partial fundoplication. BM IV = Belsey Mark IV. MHWC = Mesh hiatoplasty with cardiophrenicopexy. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

3.4.5 Secondary outcomes

Oesophageal acid exposure scores

The direct evidence available for this outcome at 3-12 months is summarised in Figure 3.15. All studies reported DeMeester scores, except for one which reported a Minaire score (Segol et al., 1989), which was subjected to sensitivity analysis by exclusion.

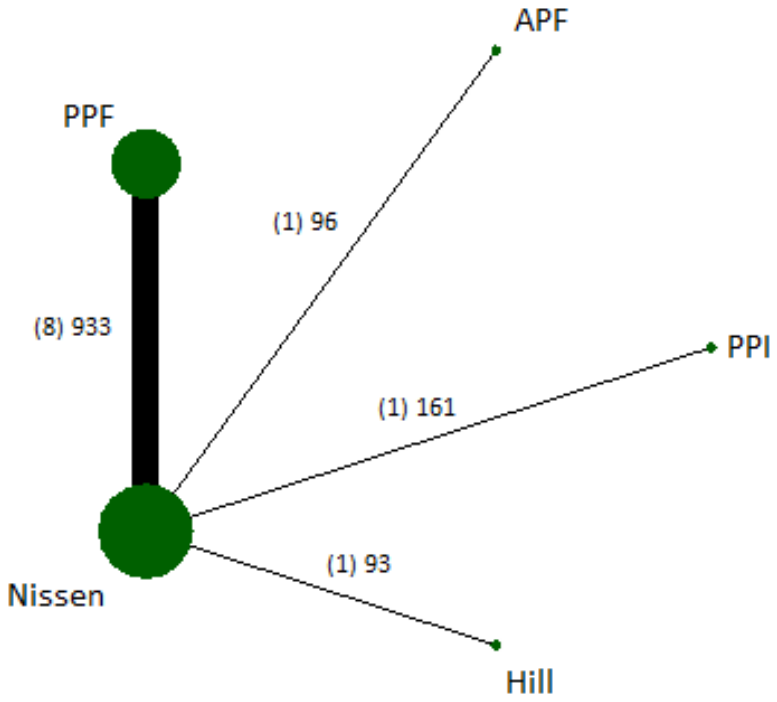


Figure 3.15 Network map of direct evidence for oesophageal acid exposure scores

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.10 reports the NMA results. PPF and Nissen patients had significantly lower oesophageal acid scores than those on PPI therapy at 3-12 months. There were no significant differences otherwise between the treatments. Predictive intervals were of moderate width, suggesting some between-study heterogeneity, but sensitivity analysis results were similar to the main analysis.

Figure 3.16 shows the fundoplication rankogram at this time point, with PPF and Nissen ranking fairly equally, followed by APF and PPI.

Table 3.10 Network meta-analysis results – Oesophageal acid exposure scores

3-12 months†				
	APF	**PPF**	**Nissen**	**Hill**
PPI	-7.57 (-17.62, 2.49)	-8.79 (-16.64, -0.95)*	-8.97 (-16.45, -1.49)*	-4.67 (-14.72, 5.39)
APF		-1.23 (-8.36, 5.90)	-1.40 (-8.13, 5.32)	2.90 (-6.61, 12.41)
PPF			-0.18 (-2.56, 2.20)	4.13 (-3.01, 11.26)
Nissen				4.31 (-2.42, 11.03)
1-5 years‡				
	APF	**PPF**	**Nissen**	
90º	-0.93 (-1.70, -0.17)*	-0.63 (-1.32, 0.07)	-1.12 (-1.81, -0.42)*	
APF		0.30 (-0.19, 0.80)	-0.18 (-0.50, 0.14)	
PPF			-0.49 (-0.86, -0.11)*	

*P < 0.05. Values in parentheses are 95% confidence intervals. †Mean difference, unit is DeMeester score value. ‡ Standardised mean difference, expressed as standard deviations. A positive value indicates that patients who underwent the treatment in the corresponding cell in the top row had higher acid exposure scores (higher acid exposure) than patients who underwent the treatment in the corresponding cell in the left hand column, and a negative value indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPI = Proton pump inhibitor. PPF = Posterior partial fundoplication.

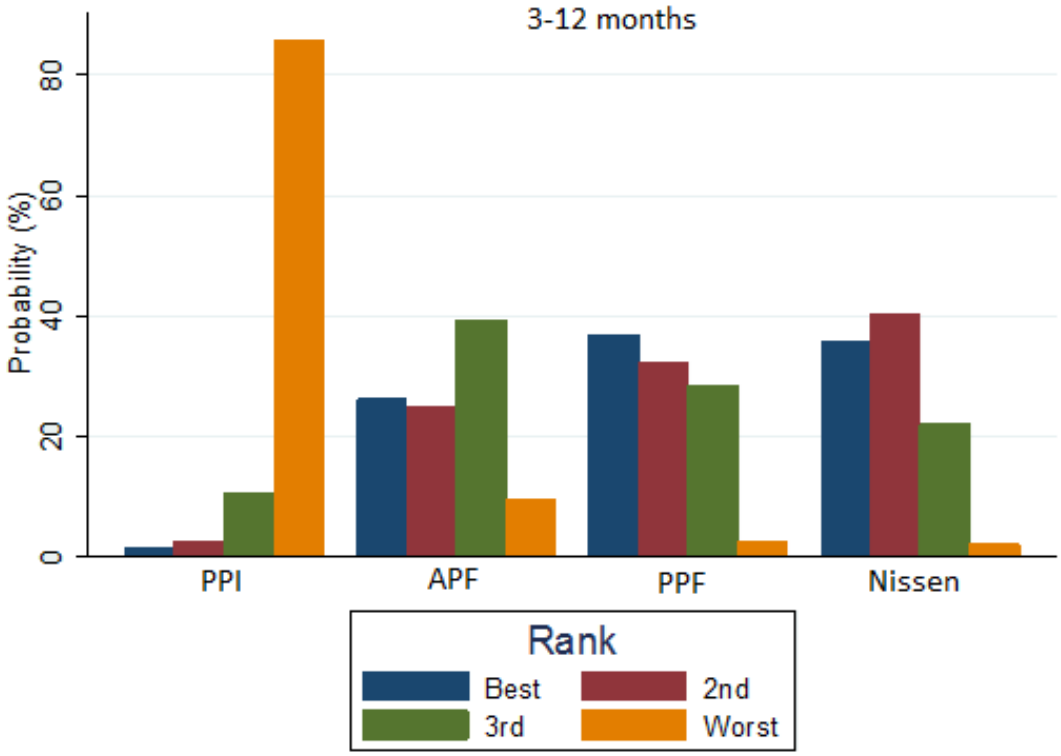


Figure 3.16 Rankogram of fundoplications according to oesophageal acid exposure scores

The probability of each included fundoplication ranking as the best, second best, third or worst treatment in the network is represented by the coloured bars. There were insufficient data for ranking at other time points, and no data for 90° fundoplication.

APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

At 1-5 year follow-up, APF and Nissen patients had significantly lower acid exposure scores than those who underwent a 90° fundoplication, and Nissen patients had significantly lower scores than PPF patients. However, these results were based on data from just four studies, and sensitivity analysis splitting the Nissen node showed different results (such as a significant decrease in acid exposure scores in PPF patients compared to APF patients and some Nissen groups). One study comparing APF with Nissen reported results at 5-10 years, and found no significant difference between the two.

Total oesophageal acid exposure time

Figure 3.17 summarises the direct evidence available at 3-12 months, and Table 3.11 reports the NMA results.

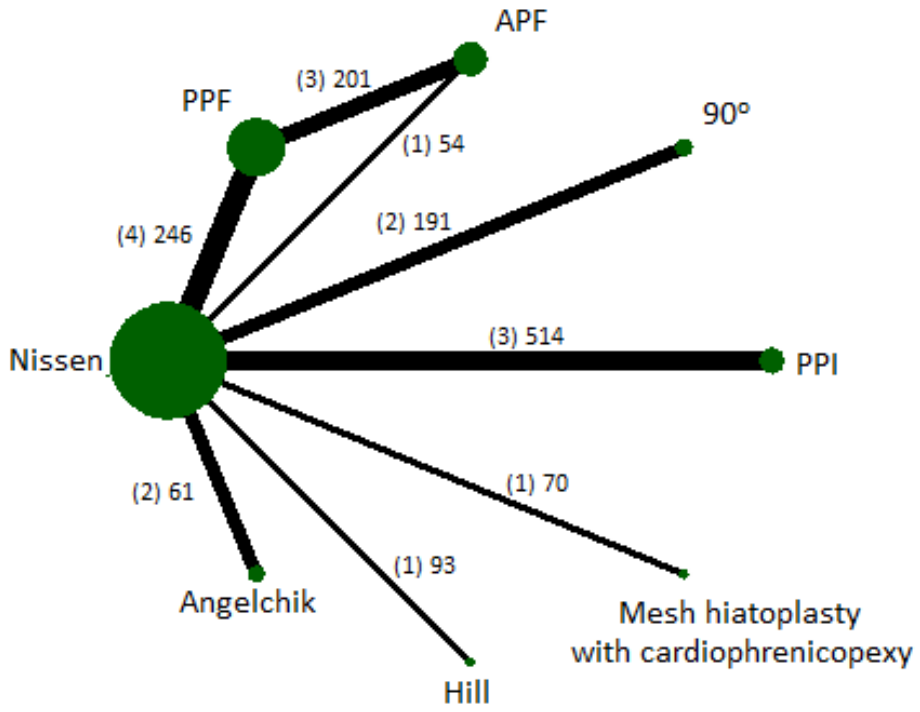


Figure 3.17 Network map of direct evidence for total oesophageal acid exposure time

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90^{o} = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.11 Network meta-analysis results – Total oesophageal acid exposure time

3-12 months							
	90º	**APF**	**PPF**	**Nissen**	**Angelchik**	**Hill**	**MHWC**
PPI	-1.35 (-4.33, 1.63)	-1.41 (-4.17, 1.35)	-2.64 (-5.11, -0.18)*	-2.25 (-4.27, -0.24)*	3.34 (0.36, 6.33)	-1.15 (-4.85, 2.55)	14.25 (10.54, 17.95)*
90º		-0.05 (-2.95, 2.84)	-1.29 (-3.91, 1.33)	-0.90 (-3.10, 1.30)	4.70 (1.58, 7.81)*	0.20 (-3.60, 4.01)	15.60 (11.79, 19.41)*
APF			-1.24 (-2.83, 0.36)	-0.85 (-2.73, 1.04)	4.75 (1.85, 7.66)*	0.26 (-3.38, 3.89)	15.66 (12.02, 19.29)*
PPF				0.39 (-1.04, 1.82)	5.99 (3.36, 8.62)*	1.49 (-1.93, 4.91)	16.89 (13.47, 20.31)*
Nissen					5.60 (3.39, 7.81)*	1.10 (-2.01, 4.21)	16.50 (13.39, 19.61)*
Angelchik						-4.50 (-8.31, -0.69)*	10.90 (7.09, 14.72)*
Hill							15.40 (11.00, 19.80)*
1-5 years							
	PPF	**Nissen**	**Hill**				
PPI	-1.70 (-3.86, 0.46)	-2.18 (-4.34, -0.02)*	-6.40 (-8.57, -4.22)*				
PPF		-0.48 (-0.57, -0.38)*	-4.70 (-4.95, -4.44)*				
Nissen			-4.22 (-4.46, -3.98)*				
5-10 years							
	APF	**PPF**	**Nissen**	**Angelchik**			
PPI	-1.44 (-2.86, -0.02)*	-12.78 (-14.30, -11.27)*	-1.39 (-2.81, 0.03)	-2.54 (-3.97, -1.10)*			
APF		-11.35 (-11.87, -10.82)*	0.05 (-0.01, 0.11)	-1.10 (-1.32, -0.88)*			
PPF			11.40 (10.88, 11.92)*	10.25 (9.69, 10.81)*			
Nissen				-1.15 (-1.36, -0.94)*			

*P < 0.05. Values in parentheses are 95% confidence intervals. Mean difference, unit is percentage acid exposure time (pH<4). A positive value indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher percentage exposure time

(longer duration of oesophageal acid exposure) than patients who underwent the treatment in the corresponding cell in the left hand column, and a negative value indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.
90^{o} = 90 degree fundoplication. APF = Anterior partial fundoplication. MHWC = Mesh hiatoplasty with cardiophrenicopexy. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

At 3-12 month follow-up, PPF and Nissen patients had significantly shorter total acid exposure times than those on PPI therapy, and those who underwent an Angelchik procedure had significantly longer exposure times than those who underwent any fundoplication or a Hill repair. MHWC patients had much longer acid exposure times than all other patients, including those on PPI therapy. Sensitivity analysis excluding non-fundoplication procedures revealed a significant decrease in exposure time in patients who underwent a PPF compared to those who underwent an APF. There was no evidence of significant between-study heterogeneity or inconsistency. The fundoplication rankogram at this time point is shown in Figure 3.18. PPF ranks best, followed by Nissen, 90º and APF, then PPI therapy.

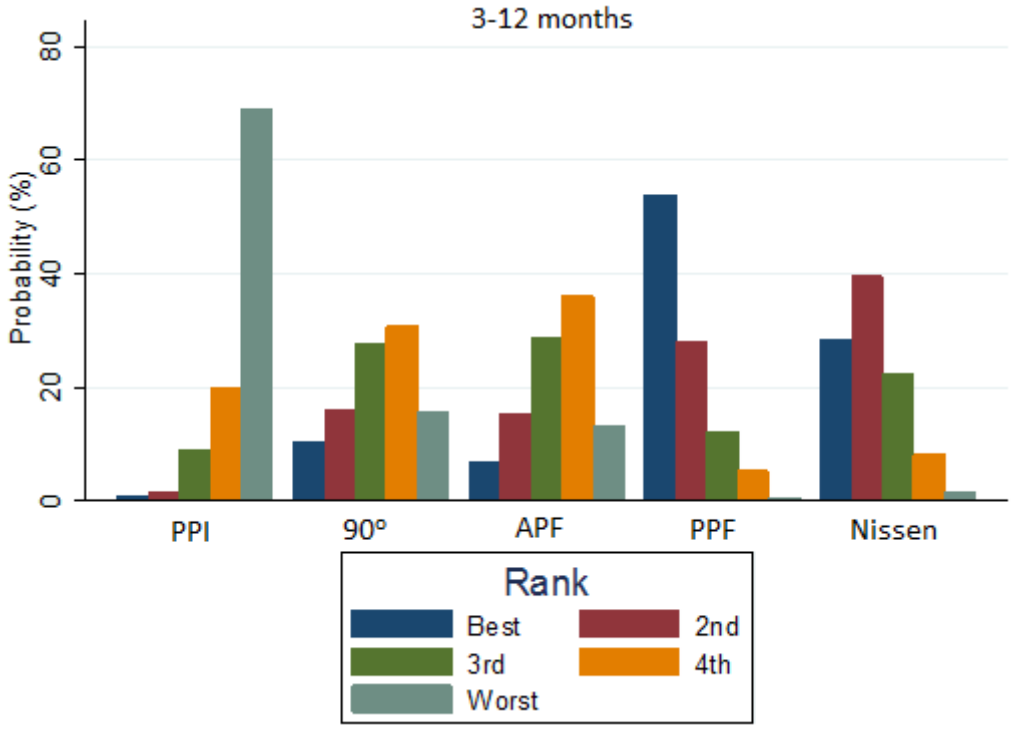


Figure 3.18 Rankogram of fundoplications according to total oesophageal acid exposure time

The probability of each included fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is represented by the coloured bars. There were insufficient data for ranking at other time points.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

At 1-5 years, Hill repair patients had significantly shorter total exposure times than all others, though data were only available for three other treatments from four RCTs (each comparison with data from only one study). Nissen patients also had significantly shorter exposure times in comparison with PPF and PPI patients. Sensitivity analysis splitting the Nissen node according to bougie use and short gastric artery division/perseveration revealed a significant decrease in acid exposure time in patients who underwent a PPF in comparison with PPI, but results were otherwise similar. There were insufficient data at this time point to calculate rankings, predictive intervals or inconsistency factors.

At 5-10 year follow-up, PPF patients had significantly shorter acid exposure times than all others. Those who underwent an Angelchik procedure had significantly shorter exposure times than all others except PPF patients. APF patients had significantly shorter times than those on PPI therapy. These results were however based on data from just four RCTs, and there were insufficient data available to statistically assess heterogeneity.

Dilatation for dysphagia

The direct evidence available at short-term follow-up is summarised in Figure 3.19, and NMA results are shown in Table 3.12.

Apart from PPF patients being significantly less likely to undergo dilatation for dysphagia than those who underwent a Nissen or Hill procedure, there were no differences between the groups at both time points with available data (up to 5 years follow-up). However, data were extremely heterogeneous with very wide confidence and predictive intervals. There was no evidence of inconsistency between the direct and indirect evidence in this outcome's networks. Figure 3.20 summarises the fundoplication rankings, which show PPF being second only to PPI therapy, followed by Nissen and APF.

One study comparing Nissen with Anglechik reported results at 5-10 years, with patients who underwent a Nissen being significantly less likely to undergo dilatation for dysphagia.

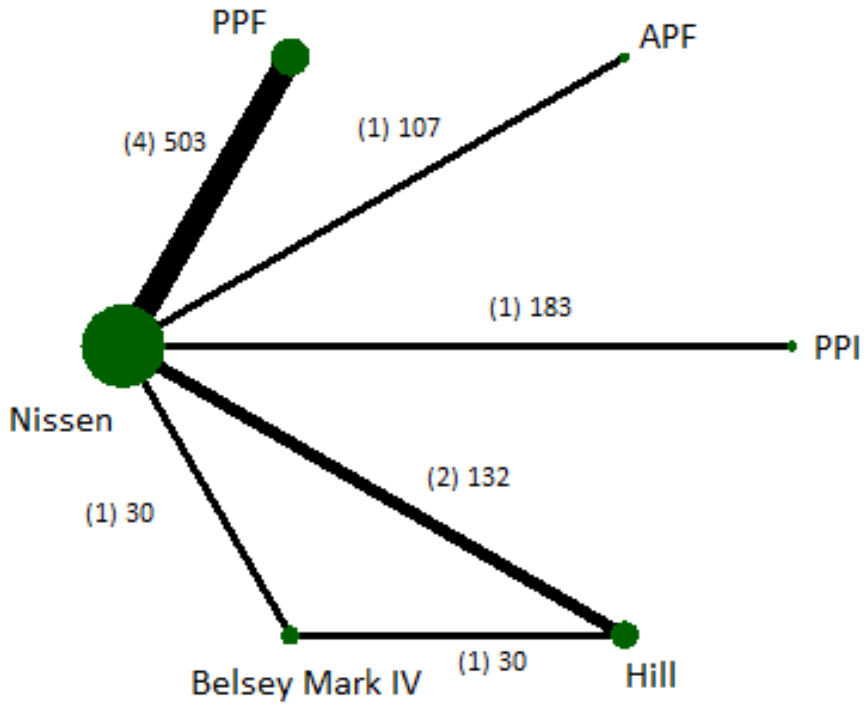


Figure 3.19 Network map of direct evidence for dilatation for dysphagia rate

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.12 Network meta-analysis results – Dilatation for dysphagia rate

3-12 months					
	APF	**PPF**	**Nissen**	**BM IV**	**Hill**
PPI	28.52 (0.36, 2230.42)	3.42 (0.16, 73.87)	9.51 (0.50, 179.04)	11.30 (0.22, 568.51)	26.72 (0.91, 781.95)
APF		0.12 (0.00, 3.41)	0.33 (0.01, 8.37)	0.40 (0.01, 24.83)	0.94 (0.02, 35.30)
PPF			2.78 (1.12, 6.92)*	3.31 (0.21, 51.75)	7.82 (1.17, 52.32)*
Nissen				1.19 (0.09, 15.92)	2.81 (0.53, 14.90)
BM IV					2.36 (0.21, 26.81)
1-5 years					
	PPF	**Nissen**	**REY DD**	**MHWC**	
APF	2.73 (0.43, 17.37)	2.95 (0.69, 12.55)	0.36 (0.01, 10.44)	0.54 (0.02, 15.98)	
PPF		1.08 (0.34, 3.43)	0.13 (0.01, 3.41)	0.20 (0.01, 5.22)	
Nissen			0.12 (0.01, 2.55)	0.18 (0.01, 3.92)	
REY				1.48 (0.02, 109.46)	
DD					

*P < 0.05. Values in parentheses are 95% confidence intervals. Unit is odds ratio. A value >1 indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher dilatation for dysphagia rate than patients who underwent the treatment in the corresponding cell in the left hand column, and a value <1 indicates the opposite. Missing treatments/time points mean no data available at this follow-up time point.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. BM IV = Belsey Mark IV. MHWC = Mesh hiatoplasty with cardiophrenicopexy. REY DD = Roux-en-Y duodenal diversion. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

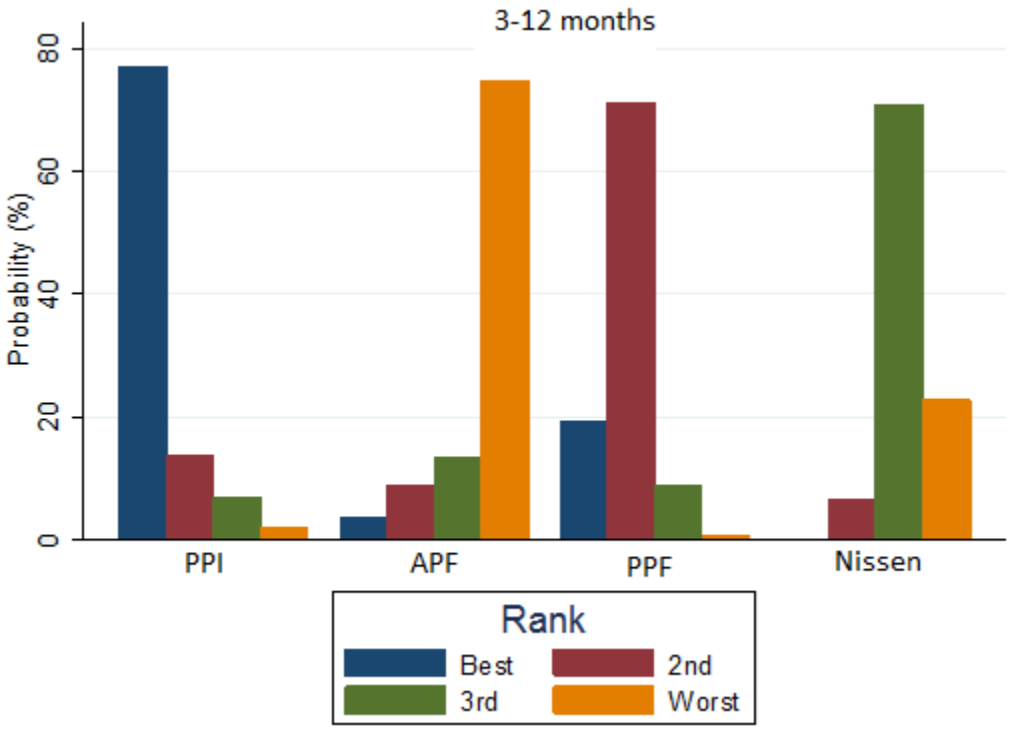


Figure 3.20 Rankogram of fundoplications according to dilatation for dysphagia rate

The probability of each included fundoplication ranking as the best, second best, third or worst treatment in the network is represented by the coloured bars. There were insufficient data for ranking at other time points, and no data for 90^{o} fundoplication.

APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Reoperation

Figure 3.21 summarises the direct evidence at 3-12 months for this outcome and Table 3.13 reports the NMA results. PPF patients were significantly less likely to require a reoperation by 5 years postoperatively compared to those who underwent a Nissen fundoplication. There was no evidence of significant between-study heterogeneity for this comparison. There were no significant differences otherwise between any of the groups at any time points. The fundoplication rankogram for this time point is shown in Figure 3.22, with PPF being >90% likely to rank as the best treatment.

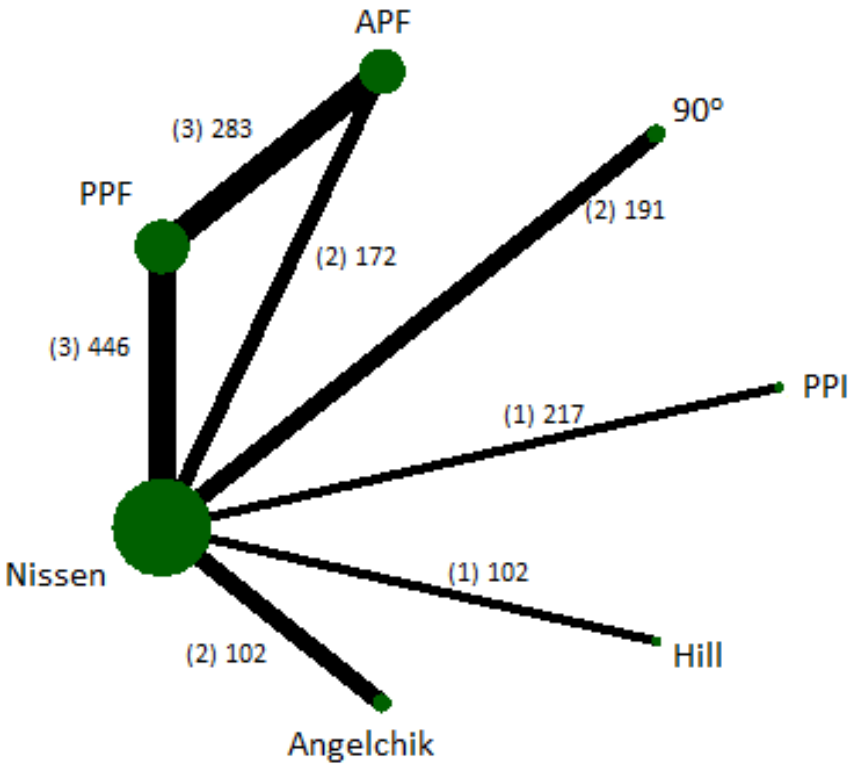


Figure 3.21 Network map of direct evidence for reoperation rate

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90° = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.13 Network meta-analysis results – Reoperation rate

3-12 months						
	90º	**APF**	**PPF**	**Nissen**	**Angelchik**	**Hill**
PPI	1.00 (0.01, 114.98)	0.86 (0.01, 85.69)	0.34 (0.00, 30.09)	0.99 (0.01, 71.06)	3.67 (0.03, 461.71)	0.81 (0.01, 121.91)
90º		0.87 (0.06, 13.10)	0.34 (0.03, 4.20)	1.00 (0.12, 7.98)	3.68 (0.17, 79.62)	0.81 (0.03, 23.23)
APF			0.39 (0.09, 1.72)	1.15 (0.21, 6.35)	4.25 (0.25, 73.29)	0.94 (0.04, 21.57)
PPF				2.94 (0.73, 11.76)	10.84 (0.76, 155.72)	2.39 (0.12, 46.79)
Nissen					3.69 (0.38, 35.70)	0.81 (0.06, 11.30)
Angelchik						0.22 (0.01, 7.12)

1-5 years							
	APF	**PPF**	**Nissen**	**Angelchik**	**REY DD**	**Hill**	**MHWC**
90º	1.14 (0.26, 4.98)	0.27 (0.08, 0.96)*	0.80 (0.25, 2.51)	1.52 (0.10, 23.22)	0.15 (0.01, 3.94)	0.69 (0.03, 14.01)	0.62 (0.10, 3.77)
APF		0.23 (0.07, 0.79)*	0.70 (0.28, 1.75)	1.33 (0.10, 18.61)	0.13 (0.01, 3.21)	0.60 (0.03, 11.33)	0.54 (0.10, 2.88)
PPF			2.97 (1.34, 6.56)*	5.67 (0.42, 76.01)	0.54 (0.02, 13.19)	2.56 (0.14, 46.45)	2.31 (0.46, 11.47)
Nissen				1.91 (0.16, 22.63)	0.18 (0.01, 4.02)	0.86 (0.05, 14.02)	0.78 (0.19, 3.13)
Angelchik					0.10 (0.00, 5.00)	0.45 (0.01, 18.70)	0.41 (0.02, 6.94)
REY DD						4.73 (0.07, 304.95)	4.27 (0.14, 127.18)
Hill							0.90 (0.04, 20.39)

5-10 years		
	PPF	**Nissen**
APF	0.17 (0.02, 1.54)	0.72 (0.28, 1.84)
PPF		4.17 (0.38, 45.18)

Table 3.13 continued

>10 years		
	PPF	**Nissen**
APF	0.44 (0.02, 11.06)	0.44 (0.03, 6.04)
PPF		1.00 (0.15, 6.62)

*P < 0.05. Values in parentheses are 95% confidence intervals. Unit is odds ratio. A value >1 indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher reoperation rate than patients who underwent the treatment in the corresponding cell in the left hand column, and a value <1 indicates the opposite. Missing treatments mean no data available at this follow-up time point. 90^{o} = 90 degree fundoplication. APF = Anterior partial fundoplication. MHWC = Mesh hiatoplasty with cardiophrenicopexy. REY DD = Roux-en-Y duodenal diversion. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

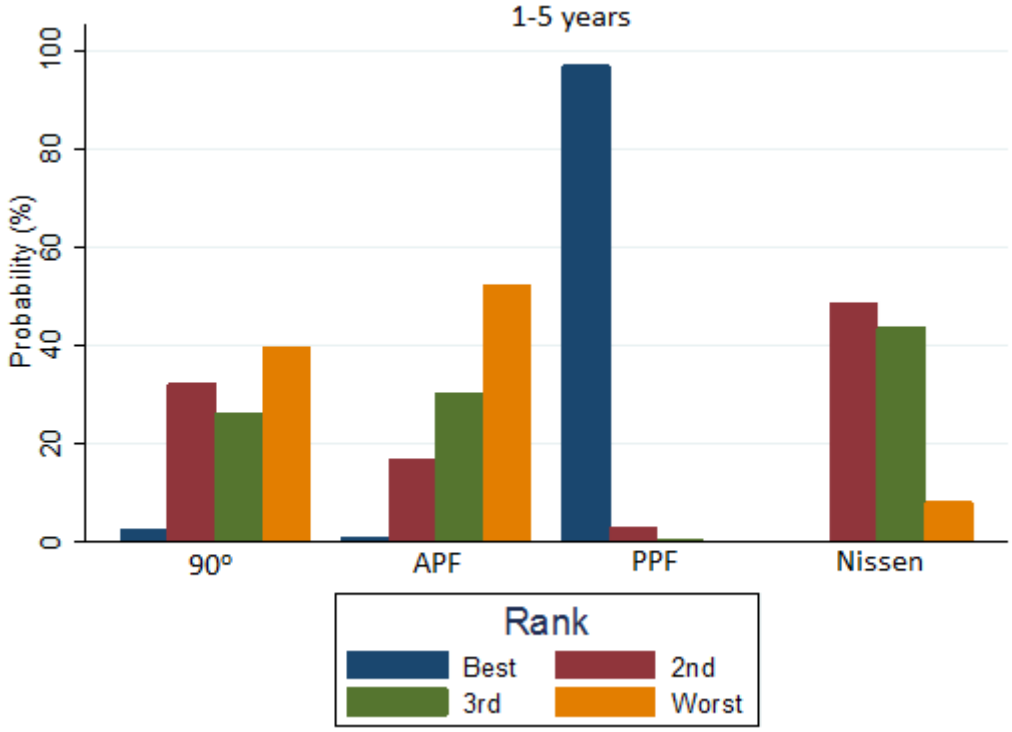


Figure 3.22 Rankogram of fundoplications according to reoperation rate

The probability of each included fundoplication ranking as the best, second best, third or worst treatment in the network is represented by the coloured bars. There were no significant differences between the treatments at all other time points, so rankograms were not calculated.

90º = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Postoperative complications

Figure 3.23 summarises the direct evidence available for this outcome for both the main analysis, and the sensitivity analysis splitting the Nissen node according to bougie use and short gastric vessel division/preservation. None of the RCTs investigating PPI therapy reported complications in that group, so PPI was only included as a reference treatment to enable its use for indirect evidence. Allowing for this, there was no significant difference between any of the surgical procedures (Table 3.14).

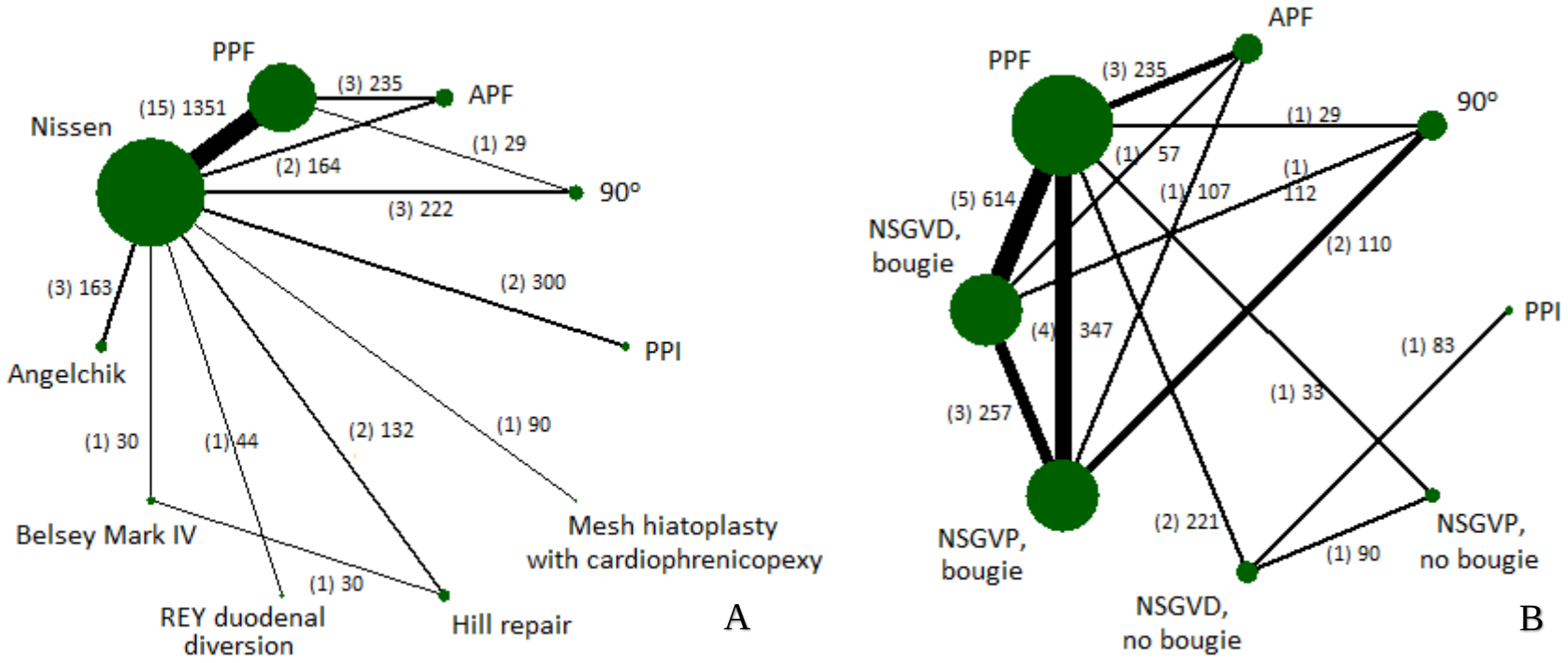


Figure 3.23 Network map of direct evidence for postoperative complications

A – main analysis, including all procedures with data for this outcome. B – sensitivity analysis (Nissen node split into four groups and non-fundoplication procedures excluded). 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

90° = 90 degree fundoplication. APF = Anterior partial fundoplication. NSGVD = Nissen with short gastric vessel division. NSGVP = Nissen with short gastric vessel preservation. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Table 3.14 Network meta-analysis results – Postoperative complications

3-12 months						
	90º	**APF**	**PPF**	**Nissen**	**Angelchik**	**BM IV**
PPI	9.54 (1.00, 91.34)	31.60 (3.33, 300.02)*	22.37 (2.77, 180.78)*	15.02 (1.94, 116.09)*	19.52 (2.01, 189.80)*	13.08 (0.80, 214.55)
90º		3.31 (0.87, 12.65)	2.35 (0.83, 6.66)	1.58 (0.60, 4.12)	2.05 (0.51, 8.17)	1.37 (0.16, 11.63)
APF			0.71 (0.28, 1.77)	0.48 (0.19, 1.22)	0.62 (0.16, 2.43)	0.41 (0.05, 3.47)
PPF				0.67 (0.44, 1.03)	0.87 (0.29, 2.58)	0.58 (0.08, 4.14)
Nissen					1.30 (0.48, 3.52)	0.87 (0.13, 5.87)
Angelchik						0.67 (0.08, 5.77)

3-12 months (continued)			
	REY DD	**Hill**	**MHWC**
PPI	15.02 (1.17, 193.40)*	19.24 (1.78, 207.56)*	9.33 (0.60, 146.02)
90º	1.58 (0.26, 9.61)	2.02 (0.43, 9.50)	0.98 (0.12, 7.79)
APF	0.48 (0.08, 2.87)	0.61 (0.13, 2.83)	0.30 (0.04, 2.33)
PPF	0.67 (0.14, 3.30)	0.86 (0.24, 3.12)	0.42 (0.06, 2.76)
Nissen	1.00 (0.22, 4.63)	1.28 (0.38, 4.31)	0.62 (0.10, 3.91)
Angelchik	0.77 (0.12, 4.78)	0.99 (0.20, 4.74)	0.48 (0.06, 3.87)
BM IV	1.15 (0.10, 13.27)	1.47 (0.23, 9.31)	0.71 (0.05, 10.10)
REY DD		1.28 (0.18, 9.05)	0.62 (0.06, 6.80)
Hill			0.48 (0.05, 4.39)

*P < 0.05. Values in parentheses are 95% confidence intervals. Unit is odds ratio. A value >1 indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher postoperative complication rate than patients who underwent the treatment in the corresponding cell in the left hand column, and a value <1 indicates the opposite. Missing treatments mean no postoperative complication rate data available.

90^{o} = 90 degree fundoplication. APF = Anterior partial fundoplication. MHWC = Mesh hiatoplasty with cardiophrenicopexy. BM IV = Belsey Mark IV. MHWC = Mesh hiatoplasty with cardiophrenicopexy. REY DD = Roux-en-Y duodenal diversion. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor.

Gas bloat syndrome

Figures 3.24 and 3.25 summarise the direct evidence available at 3-12 months, for rates and scores respectively. Most studies reported abdominal bloating or hyperflatulence only, and these data were not included.

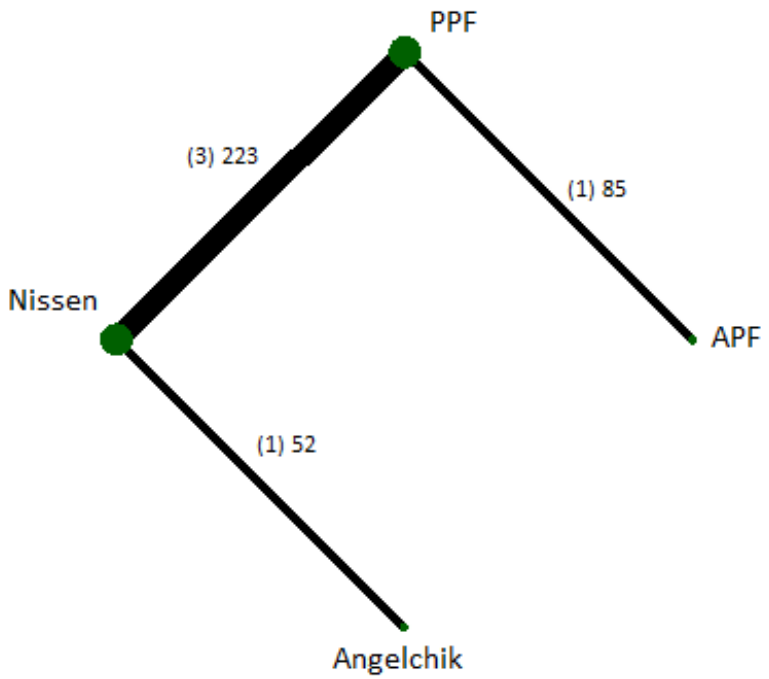


Figure 3.24 Network map of direct evidence for gas bloat rate

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication.

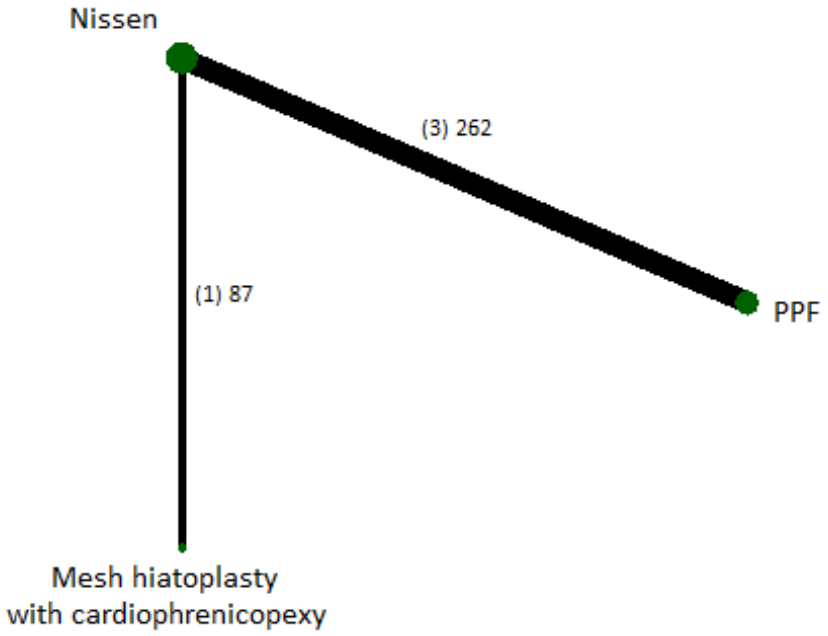


Figure 3.25 Network map of direct evidence for gas bloat scores

3-12 month data. 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. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs.

PPF = Posterior partial fundoplication.

Tables 3.15 and 3.16 show the NMA results for rate and score data respectively. There were no significant differences between the groups at any of the time points, although there was a relative paucity of data for this outcome (Table 3.3). Predictive intervals were very wide, suggesting significant between-study heterogeneity. Pairwise meta-analysis and sensitivity analysis also showed no significant differences.

Table 3.15 Network meta-analysis results – Gas bloat rate

3-12 months		
	PPF	**Nissen**	**Angelchik**
APF	1.36 (0.33, 5.66)	2.70 (0.50, 14.66)	0.34 (0.01, 12.76)
PPF		1.98 (0.80, 4.94)	0.25 (0.01, 7.00)
Nissen			0.13 (0.01, 3.11)
1-5 years		
	Nissen	**Angelchik**
PPF	1.66 (0.69, 3.99)	1.52 (0.43, 5.40)
Nissen		0.92 (0.28, 3.00)

*P < 0.05. Values in parentheses are 95% confidence intervals. Unit is odds ratio. A value >1 indicates that patients who underwent the treatment in the corresponding cell in the top row had a higher gas bloat rate than patients who underwent the treatment in the corresponding cell in the left hand column, and a value <1 indicates the opposite. Missing treatments/time points mean no data available.

APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication

Table 3.16 Network meta-analysis results – Gas bloat scores

3-12 months		
	Nissen	**MHWC**
PPF	1.95 (-1.79, 5.69)	1.90 (-5.55, 9.34)
Nissen		-0.06 (-6.50, 6.38)
1-5 years		
	Nissen	**MHWC**
PPF	0.09 (-0.38, 0.55)	-0.23 (-0.87, 0.40)
Nissen		-0.32 (-0.76, 0.12)

*P < 0.05. Values in parentheses are 95% confidence intervals. Standardised mean difference, expressed as standard deviations. A positive value indicates that patients who underwent the treatment in the corresponding cell in the top row had higher scores (more gas bloat) than patients who underwent the treatment in the corresponding cell in the left hand column, and a negative value indicates the opposite. Missing treatments/time points mean no data available.

MHWC = Mesh hiatoplasty with cardiophrenicopexy PPF = Posterior partial fundoplication.

3.4.6 Cluster plots of benefit and harm

SUCRA clustered ranking plots are shown in Figure 3.26. Across all time points with sufficient data to enable this analysis, PPF was the only treatment which consistently ranked well in terms of reflux and dysphagia (top right quadrant of the graph).

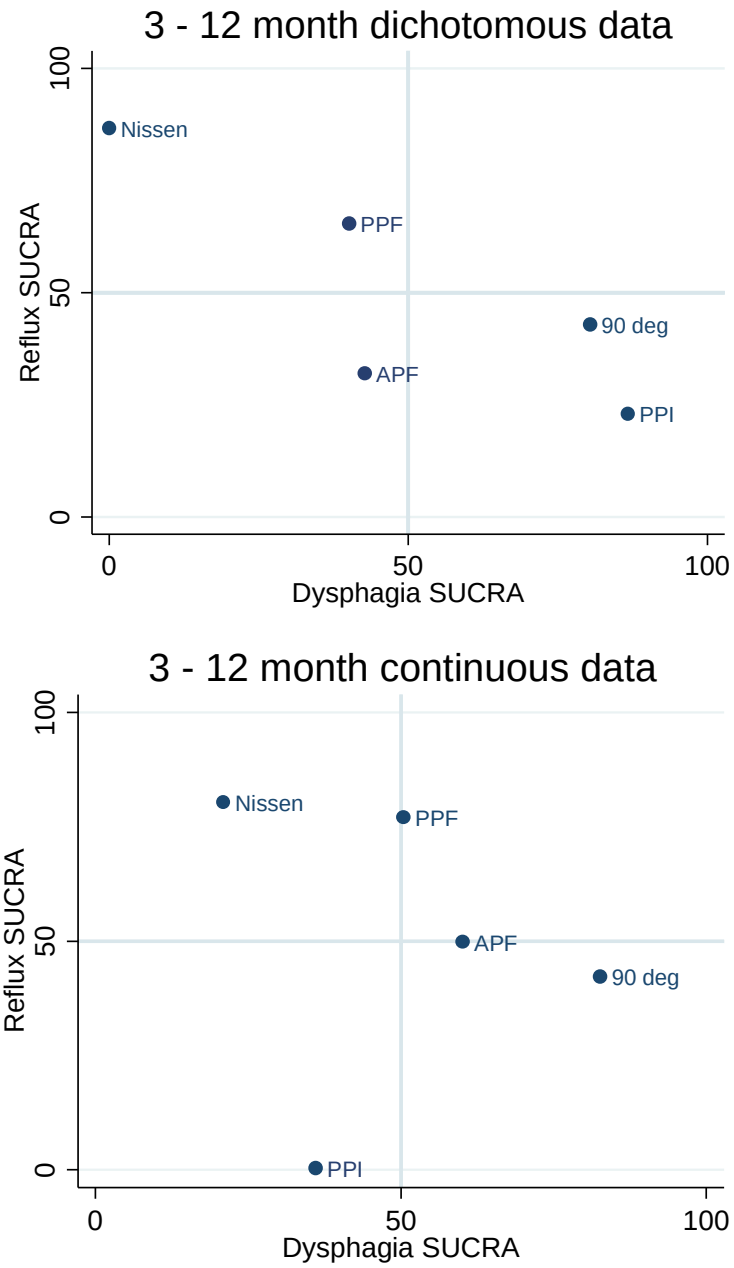
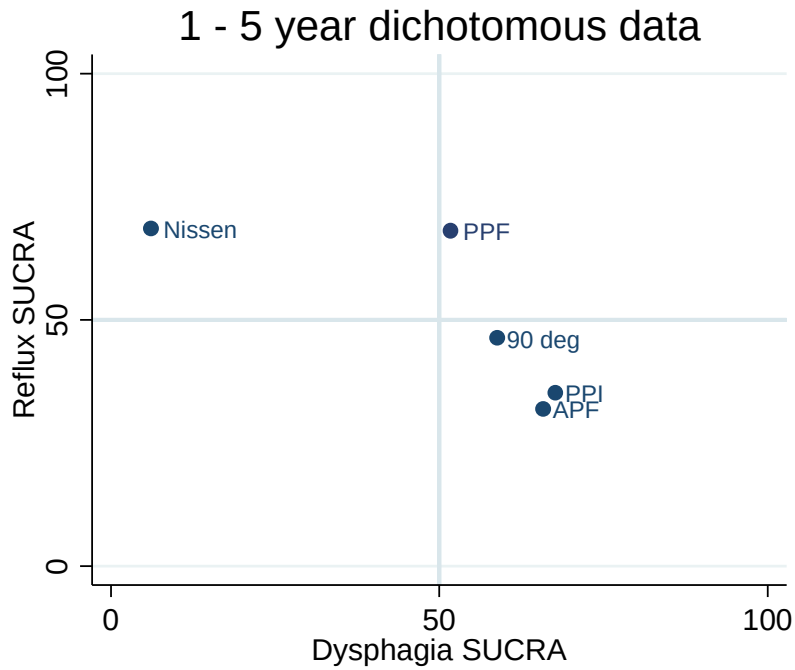


Figure 3.26 Clustered ranking plots of main treatments at different time points, according to efficacy of reflux control and incidence of dysphagia (continued on next page)



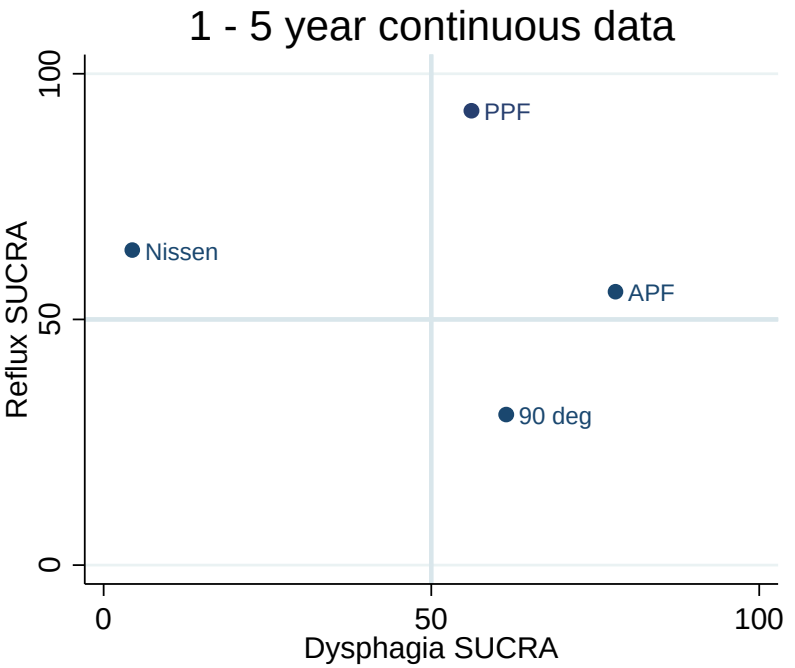


Figure 3.26 Continued - Clustered ranking plots of main treatments at different time points, according to efficacy of reflux control and incidence of dysphagia (continued on next page)

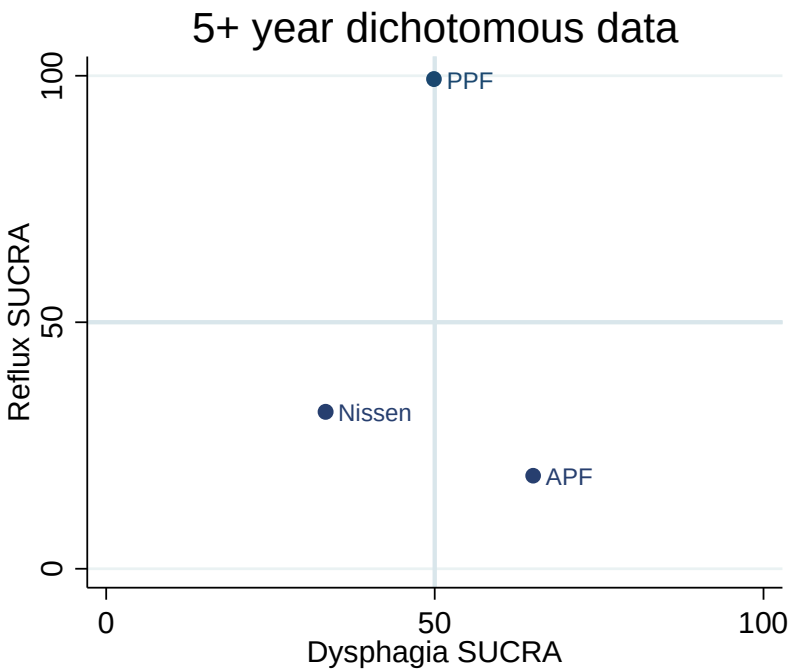


Figure 3.26 Continued - Clustered ranking plots of main treatments at different time points, according to efficacy of reflux control and incidence of dysphagia

Plots for dichotomous and continuous data analyses presented separately. The SUCRA value for each treatment is derived from the mean ranking in the network. A SUCRA value of 100 corresponds to a 100% probability of that treatment ranking first for that outcome, and a value of 0 corresponds to a 100% 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 10+ year time points were combined to enable cluster analysis.

90 deg = 90 degree fundoplication. APF = Anterior partial fundoplication. PPF = Posterior partial fundoplication. PPI = Proton pump inhibitor. SUCRA = Surface under the cumulative ranking curve.

3.5 Discussion

This NMA shows that a 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 MAs have compared PPF with NF alone (Broeders et al., 2010; Shan et al., 2010; Tan et al., 2011), concluding that PPF resulted in equivalent reflux control with less dysphagia, but these were not able to include other commonly performed procedures such as APF (Thompson and Watson, 2015). Other MAs have included PPF in a mixed "posterior" (Broeders et al., 2011; Memon et al., 2015) or "partial" (Ma et al., 2012; Varin et al., 2009) fundoplication group, and compared this to a second mixed group, with results that are difficult to interpret given the heterogeneous nature of the procedures within each group (Thompson and Watson, 2015). All of these prior MAs included a small number of RCTs (<12) as only direct comparisons could be used. Most only used the data reported at latest follow-up from each RCT, meaning that the analysis contained short and long term results from different patients. This introduces another source of heterogeneity as the prevalence of symptoms such as dysphagia changes considerably over time (Fuchs et al., 2014).

The NMA methodology used in the present study has allowed much more RCT data to be included, with each procedure analysed simultaneously as a separate group in a manner that fully respects randomisation (Caldwell et al., 2005). The use of all available direct and indirect evidence substantially increased the precision of the effect estimates. Analysing data from different follow-up time points separately also eliminated an important source of heterogeneity and allowed for the determination of outcome measures over time. These features substantially increase the external validity and clinical applicability of the results in comparison with previous reviews.

Patient-reported symptoms and scores were used to assess all primary and several secondary outcomes in this review to enable a pragmatic evaluation of the procedures (Grant et al., 2013). More objective tools such as pH monitoring and endoscopy have traditionally been regarded as the best methods of assessing reflux control after surgery for GORD (Demeester et al., 1974), and manometry and mechanical studies have been used to assess side effects such as dysphagia (Booth et al., 2008). However there is evidence that the results of such investigations correlate poorly with clinical outcome following surgery (Anvari et al., 2011; Mathew et al., 1997; O'Boyle et al., 2002; Shaw et al., 2010; Walker et al., 1992). Furthermore, well patients with no substantial symptoms

are less likely to consent to further invasive tests postoperatively, which may bias the results (Cai et al., 2008).

The best measure of surgical success is relief of symptoms without side effects as reported by the patient, particularly as the indication for anti-reflux surgery is usually patient preference and symptom severity (Shaw et al., 2010). Patient-reported symptom scores have been shown to correlate best with the actual outcome as perceived by the patient (Watson et al., 2012).

This study has some potential limitations. The quality of included trials in any meta-analysis affect 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 considerably 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 concerns (Kmiot et al., 1991), may be questioned. However, this enabled the inclusion of indirect evidence from those RCTs, which increased the precision of the overall effect estimates. Furthermore, each of these older procedures were analysed as separate nodes in all analyses, and subjected to sensitivity analysis (by exclusion) to ensure that their inclusion did not influence the main findings.

Endoscopic procedures for the treatment of GORD were not included in this review even though a number have been developed over the last decade as an alternative to surgery. Although initial reports showed some promise, subsequent sham-controlled studies have generally failed to demonstrate the efficacy of these techniques (Fry et al., 2007). The placebo response in some is up to 50% (Hogan, 2006) and several techniques were subsequently withdrawn from the market because of safety and durability concerns (Hogan, 2006). In view of this endoscopic anti-reflux procedures were not included in as specified *a priori* in the review protocol (Amer et al., 2014).

Current US (Stefanidis et al., 2010) and European (Fuchs et al., 2014) guidelines suggest that the choice of anti-reflux 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 NMA, which incorporates the results of over 50 RCTs involving more than 5300 patients, challenges such guidelines by showing that a PPF provides the best balance of reflux control and dysphagia in comparison with all other anti-reflux procedures and medical therapy, and that this effect is durable. Future research should be directed at comparing novel procedures to PPF and improving the amount of long term follow-up data available for existing procedures, such as through the use of registries.

3.6 Conclusion

This review was able to incorporate the entirety of available RCT evidence on the surgical management of GORD, using NMA methodology. This has allowed for a simultaneous assessment and ranking of all the described interventions against clinically relevant measures of benefit and harm, which was not possible previously using standard MA methods. This methodology can be applied to other surgical research synthesis scenarios where multiple treatment options exist.

The results of this review show that a PPF provides the best balance of long-term, durable reflux control with less dysphagia, compared to other treatments. While other procedures may be more suitable in carefully selected patients, PPF should be considered the standard intervention for the surgical management of GORD in adults.

CHAPTER FOUR

Bias in surgical randomised trials: a meta-epidemiological study using laparoscopic versus open surgery as an example

My contribution to this chapter

This project was conceived by my supervisors (JLM, GPH and MDS) and myself. I drafted the project plan and revised it in conjunction with my supervisors. I designed the search strategy and performed all steps of the systematic search and review update process, and selected and extracted data from all identified eligible trials, with duplication by Samuel Grainger and Choo Khoo, two part-time research assistants employed for this project. Peter McCall assisted with data entry on a contract basis in preparation for analysis. I performed all of the analysis with expert advice from GPH. All drafts and the final text of this chapter were written by myself, with revisions in conjunction with my supervisors.

4.1 Chapter summary

Blinding, random sequence generation, and allocation concealment are established strategies to minimise bias in RCTs. Meta-epidemiological studies of drug trials have demonstrated exaggerated treatment effects in RCTs where such methods were not employed. As blinding is more difficult in surgical trials it is important to determine whether this applies to them. This study investigated whether lack of blinding, and other potential sources of bias in trial design, have a systematic effect on surgical RCT outcomes, using trials comparing laparoscopic and open surgery as an example. The Cochrane Database of Systematic Reviews was searched for systematic reviews of RCTs that compared laparoscopic and open abdominal surgical procedures. Each review was then scrutinised to determine whether at least one of the included trials was blinded. Eligible reviews were updated and individual RCTs retrieved. Extracted data included the primary outcomes of interest (length of stay and complications), secondary outcomes and a risk of bias assessment. A pairwise meta-analysis was performed for each procedure comparing laparoscopic and open surgery. Serial meta-regression was then used to determine how each bias-minimisation measure influences the size of the treatment effect within each procedure. The resulting coefficients were meta-analysed to obtain an overall difference between trials that employed bias-

minimisation strategies, and those that did not. Five hundred and ninety six full-text articles were identified, and data from 316 RCTs were included, reporting on eight different procedures. Patient-blinded RCTs reported a smaller difference in length of stay between laparoscopic and open groups (difference of standardised mean differences (DSMD) -0.36 (CI) -0.73, 0.00)), and complications (ratio of odds ratios (ROR) 0.76 (CI 0.61, 0.93)). Blinding of postoperative carers and outcome assessors had similar effects on reported outcomes. This study shows that lack of blinding significantly alters the treatment effect estimates of RCTs comparing laparoscopic and open surgery, and may lead to erroneous conclusions. Blinding should be implemented in procedural RCTs where possible to avoid systematic bias.

4.2 Introduction

RCTs are well established as the ideal trial design for assessing the benefits and harms of healthcare interventions, as they can account for unmeasured confounders (Stirrat et al., 1992). This is important in the context of novel surgical techniques, which should undergo rigorous scientific validation prior to widespread uptake (Meakins, 2009; Potter et al., 2014; Russell, 1995). The objectiveness and validity of RCTs is critical as their results and the conclusions of subsequent meta-analyses substantially influence evidence-based clinical practice and health policy (Moher et al., 1998).

One challenge for the validity of RCTs is the potential for outcome assessments of interventions to systematically deviate from the true effect size because of bias arising from preconceptions and predispositions such as optimism, the placebo effect and observer bias (Hrobjartsson et al., 2012; Schulz and Grimes, 2002). The different terms used to describe these biases, their sources and relevance to surgical RCTs in particular have been detailed in Chapter 1, as well as strategies to counter them such as blinding, random sequence generation and allocation concealment.

There are several examples of novel procedural interventions where early non-blinded RCTs appeared to show superiority over established treatments, whereas subsequent appropriately blinded RCTs concluded that the novel procedure is no more effective than the established treatment or a sham procedure. Renal artery denervation for the treatment of hypertension (Shun-Shin et al., 2014), endoscopic sphincterotomy for pain after cholecystectomy (Cotton et al., 2014),

embryonic dopamine neuron implantation for severe Parkinson's (McRae et al., 2004) and arthroscopic partial meniscectomy for degenerative tears (Sihvonen et al., 2013) are all recent examples of this.

Research methodology studies have shown that lack of blinding in RCTs results in an exaggeration of the treatment effect of interventions. In serial systematic reviews of RCTs with both blinded and non-blinded outcome assessors, Hróbjartsson et al demonstrated an exaggerated treatment effect of between 27% and 68% with respect to binary (Hrobjartsson et al., 2012), continuous (Hrobjartsson et al., 2013) and time-to-event outcomes (Hrobjartsson et al., 2014). However, these systematic reviews included data from fewer than 25 RCTs each. Meta-epidemiological studies can incorporate a much greater number of studies and therefore much more data (Stirrat et al., 1992). All such studies published to date have included trials investigating a wide range of treatments across a range of disciplines. The effect of blinding and other bias-minimisation measures specifically on RCTs of surgical procedures has not been examined.

Laparoscopic surgery was first introduced into general surgical practice in the 1980s, having first been described by Georg Kelling in 1901 (Schollmeyer et al., 2007), and almost 30 years after its introduction to gynaecological practice (Cuschieri, 1989). It has been argued that no other development has had such a dramatic and pivotal impact on surgery worldwide (Neugebauer et al., 1995). Many general surgical procedures have subsequently transitioned from an open to a laparoscopic approach with the latter often becoming accepted as the 'standard of care' (Russell, 1995) before definitive evidence from well-designed RCTs (Neugebauer et al., 1991). The added cost of laparoscopic surgery is widely considered to be offset by benefits such as shorter postoperative hospitalisation, quicker return to work, less postoperative pain and fewer postoperative complications (Cuschieri et al., 1990). This is in part based on MAs of RCTs, most of which were non-blinded (McCulloch et al., 2002).

This chapter reports the results of a meta-epidemiological study using individual trial data to investigate whether lack of blinding and other potential sources of bias in surgical RCT design systematically affect subjective trial outcomes, using RCTs comparing laparoscopic and open approaches to general surgical operations as an example.

4.3 Methods

A study protocol was prepared and agreed upon *a priori*.

4.3.1 Search strategy and selection criteria

Any abdominal surgical procedure which is performed both laparoscopically and open was included, where the two approaches have been compared in RCTs and where at least one of those trials was blinded. A blinded RCT was defined as a trial where the patients, healthcare staff, data collectors, outcome assessors, and/or data analysts were unaware of the patient's assigned treatment (Fergusson et al., 2004; Haahr and Hrobjartsson, 2006; Montori et al., 2002) for at least the duration of the patient's postoperative hospital stay. The definitions for these blinding categories were as follows:

- Patients were defined as the individuals who were assigned to one of the approaches.
- Healthcare staff were defined as the nurses, doctors and other personnel (apart from the operating surgeon) who cared for the patients during the study period.
- Data collectors were defined as the individuals who collected data for the study outcomes (e.g. administered a questionnaire on postoperative pain).
- Outcome assessors were defined as the individuals who decided if a participant had attained or suffered the outcome of interest (e.g. return of intestinal function or postoperative complications).
- Data analysts were defined as the individuals who conducted the data analysis.

All randomised and quasi-randomised trials were included. Quasi-randomisation was defined as the use of methods such as alternation, or assignment on the basis of date of birth, record number, day of admission or similar (Higgins and Green, 2011). No language, publication status or year of publication restrictions were applied. All citations were in English, as translated by the databases. Abstracts and full texts in French, German and Japanese were able to be translated by the data extractors. Studies in other languages were translated using Google translate (Jackson et al., 2019). Non-randomised trials and studies investigating single-incision laparoscopic or natural orifice endoscopic approaches were excluded.

The systematic search for eligible trials was conducted in three stages.

Eligible procedure search

Firstly, the Cochrane Library was searched from inception to March 2015 using a structured strategy (Appendix D1) to identify systematic reviews where a laparoscopic and open approach to an abdominal general surgical procedure was compared. The Cochrane Library search included the following resources:

1. The Cochrane Database of Systematic Reviews.
2. The Database of Abstracts of Reviews of Effects.
3. The Cochrane Methodology Register.
4. The Health Technology Assessment (HTA) Database.
5. The NHS Economic Evaluation Database.

The 'related articles' feature in PubMed and the reference lists of identified systematic reviews were also checked to identify further potentially relevant reviews. All potentially eligible systematic reviews were then scrutinised to determine whether at least one of the included RCTs were blinded. A list of eligible procedures was then drawn up.

All RCTs included in the identified systematic reviews assessing each procedure were checked for eligibility for this study. Lists of studies excluded from those reviews were also checked where available to determine whether any were eligible for this study. This was pertinent in several instances where the published systematic review had excluded quasi-randomised trials.

Review search update

Secondly, for each eligible procedure, the published search strategy of the most recent review was used to update the systematic search for RCTs comparing a laparoscopic and open approach, by searching the same electronic databases as the original review, or the following at a minimum: the Cochrane Library, MEDLINE and EMBASE.

If the most recent review had no available published search strategy, an alternative review for the same procedure with a published strategy was selected. The database search dates were customised to overlap with the most recent calendar year of the published reviews' searches for that procedure (e.g. if the most recent published review's search was to May 2010, the search start date was set to January 2010). The search end date for all procedures was November 2015.

The results of each search were combined in a spreadsheet and duplicate citation records were excluded. Multiple (non-duplicate) publications of the same trial were retained in case all data were not reported in both. Study protocols were also retained to aid in assessing study methodology (risk of bias assessment). Two reviewers independently screened all titles and abstracts for eligibility, then the full text of potentially eligible trials against the selection criteria. Systematic reviews identified in this update process were also retrieved, and the included and excluded studies lists checked for eligible RCTs. Disagreement was resolved by consensus and discussion with a third author when required.

Retrieval of eligible trials

Finally, procedure-specific lists of RCTs were drawn up, combining all eligible RCTs identified in either of the above two steps. These RCTs were individually retrieved and assessed for relevant outcomes before inclusion.

4.3.2 Outcome measures

Trials that reported any of the following outcomes for an eligible procedure were included. All outcomes and their definitions were agreed upon *a priori*.

Primary outcomes

1. Length of postoperative stay (in days).
2. Postoperative complication rate (as defined by trial authors).

Secondary outcomes

1. Time to recovery (number of postoperative days to return to work or usual activity as defined by trial authors).
2. Postoperative pain (measured by ordinal, visual analogue or composite scales). This outcome was divided into short-term (<4 weeks) and long-term pain (≥4 weeks) for all procedures.
3. Return of intestinal function (number of postoperative days to first passage of flatus, and first passage of bowel motion).

4.3.3 Data extraction and quality assessment

Two reviewers independently extracted and recorded data from each included RCT, including key patient and intervention characteristics and relevant outcome data, using a pre-piloted data extraction form (Appendix D2), based on the Cochrane Collaboration's Data Collection Form Template (Cochrane, 2013). Discrepancies were resolved by discussion and arbitration by a third reviewer when required.

Where studies reported both time to return to work and time to usual activity, the latter was preferentially extracted as return to employment is not universal and is influenced by the nature of each patient's occupation. Postoperative pain data reported at multiple time points for different patient numbers within one of this study's predefined time points (< and ≥ 4 weeks) were all extracted, and a 'mini' meta-analysis was performed using RevMan (Review Manager V5.3, The Nordic Cochrane Centre, Copenhagen) to obtain a summary statistic (MD) and measure of variance (standard error). These results were then entered as the data for postoperative pain (in the appropriate time subgroup) for that study. Different postoperative pain scales with an opposite direction of severity were inverted by subtracting the mean from the maximum possible value for the scale, to ensure all scales point in the same direction (Higgins and Green, 2011). Time to recovery and return of intestinal function data were converted from weeks and hours respectively into days when required to ensure data unit homogeneity.

Missing statistics such as standard deviations were calculated from reported data where possible (Higgins and Green, 2011; Hozo et al., 2005). When standard deviations could not be calculated, these were imputed using the reported standard deviations from other trials for that outcome and procedure.

Outcome data from RCTs reporting multiple laparoscopic or open arms (e.g. mini-incision and standard open, or gasless and standard laparoscopy) were combined where appropriate using the appropriate formulae (Higgins and Green, 2011). Ineligible treatment groups in multi-arm trials (such as robotic surgery) were excluded.

The reviewers also independently conducted a detailed risk of bias assessment. This was based on the Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011), with expansion of the

blinding domain into five separately assessed components to cover the blinding categories detailed earlier in Section 4.3.1. The following domains were also assessed: random sequence generation, allocation concealment, incomplete outcome data, selective outcome reporting, and other potential sources of bias (such as baseline imbalances or differential diagnostic activity). Each domain was assessed as low risk, high risk or unclear. Study protocols were used at this point where available, then excluded from subsequent steps. Disagreements were resolved by discussion or arbitration by a third reviewer where consensus could not be reached.

4.3.4 Statistical analysis

The extracted individual trial data were analysed using meta-epidemiological principles (Sterne et al., 2002) in three steps to determine the influence of each form of blinding, effective random sequence generation and allocation concealment on reported treatment effects, using the Stata (StataIC 13, StataCorp LP., College Station, Texas) statistical package and relevant commands.

Firstly, a pairwise MA was performed for each procedure to determine the difference between a laparoscopic and open approach with regards each outcome of interest, using a random effects model and the metan command (Harris et al., 2008). The effect size for continuous data were summarised as an SMD (expressed as SD). Categorical data were summarised as odds ratios. Where reported data allowed for this, an intention-to-treat analysis was used.

Secondly, binary codes were used for each study to separately denote whether each bias-minimisation measure in question (such as blinding of patients) was used (0 = measure not used or unclear/high risk, 1 = measure used or low risk), as per the risk of bias assessment. Serial meta-regression (sorted by procedure type) was then performed using the metareg command (Sharp, 1998) to determine the difference in effect estimate between studies that used each measure and those that did not, for each outcome of interest using a random effects model (White, 2011). The results of this step were summarised as DSMDs for continuous data, and RORs for categorical data.

Lastly, these meta-regression results were in turn meta-analysed using the metan command (Harris et al., 2008) across the procedures to obtain an overall difference in effect estimate between studies that used each bias-minimisation measure and those that did not, for each outcome of interest.

These results were summarised as DSMDs and RORs for continuous and categorical data respectively, and presented as forest plots with calculation of the I^2 statistic to assess statistical heterogeneity between the procedures. A summative analysis comparing studies that used any form of blinding and those that did not was also performed for primary outcomes.

Post hoc sensitivity analysis was performed where appropriate to determine the influence of the inclusion of procedures with fewer data. The results of these sensitivity analyses are reported where they are notably different to the main analysis results.

4.4 Results

4.4.1 Search results and study characteristics

Eligible procedure search

The results of the search for eligible procedures (first step of the systematic search) are summarised in Figure 4.1. Nine eligible procedures were identified through 50 systematic reviews of RCTs comparing a laparoscopic and open approach. An additional sixteen reviews were subsequently identified using Pubmed's 'related articles' feature. The procedures and the number of potentially eligible RCTs identified at this stage of the search are listed in Table 4.1.

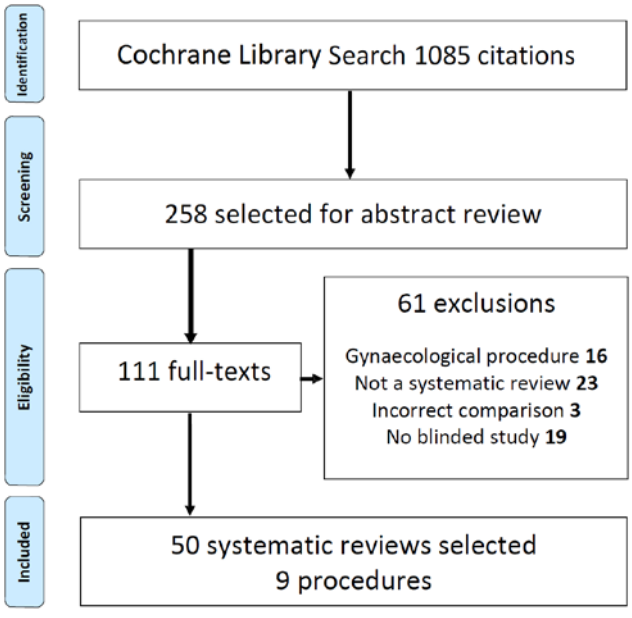


Figure 4.1 Search for eligible procedures

Table 4.1 Selected Procedures

Procedure	Number of reviews*	Number of articles†
Appendicectomy	13	85
Cholecystectomy	3	66
Colonic resection	25	74
Donor nephrectomy	4	20
Fundoplicaton	2	22
Gastric bypass	2	6
Inguinal hernia	6	84
Rectal resection	7	25
Rectopexy	4	4
Total	**66**	**386**

*This includes systematic reviews identified using PubMed's 'related articles' feature following the Cochrane Library's database search. †The number of potentially eligible papers identified through the reviews' included and excluded studies lists. These were later checked for duplicate publication and relevant outcomes (in step three) prior to inclusion.

Review search update

Table 4.2 lists the systematic reviews from which search strategies were used to update the search for each included procedure and the start date of each search. The study selection process following this is summarised in Figure 4.2 and detailed per procedure in Table 4.3. The potentially eligible RCTs identified at the conclusion of this step were then combined with those identified earlier during the search for eligible procedures.

Table 4.2 Review update strategies

Procedure	Review's search strategy used	Search start date*
Appendicectomy	(Sauerland et al., 2010)	2014
Cholecystectomy	(Keus et al., 2006)	2004
Colonic resection	(Sammour et al., 2011)	2012
Donor nephrectomy	(Wilson et al., 2011)	2013
Fundoplicaton	(Amer et al., 2014)†	2014
Gastric bypass	(Reoch et al., 2011)‡	2010
Inguinal hernia	(McCormack et al., 2003)	2009
Rectal resection	(Vennix et al., 2014)	2013
Rectopexy	(Tou et al., 2008)	2010

*Calendar year overlap with the latest published search for that procedure. Where the search strategy for the most recently published review was not available, another review's strategy for that procedure was used instead. Therefore these dates do not necessarily correlate with the search dates of the systematic reviews from which the search strategy was used. †Study protocol with a published search strategy. ‡An initial search using this review's strategy yielded over 10,000 citations, so after discussion with subject experts the following terms were dropped: weight loss, obesity.

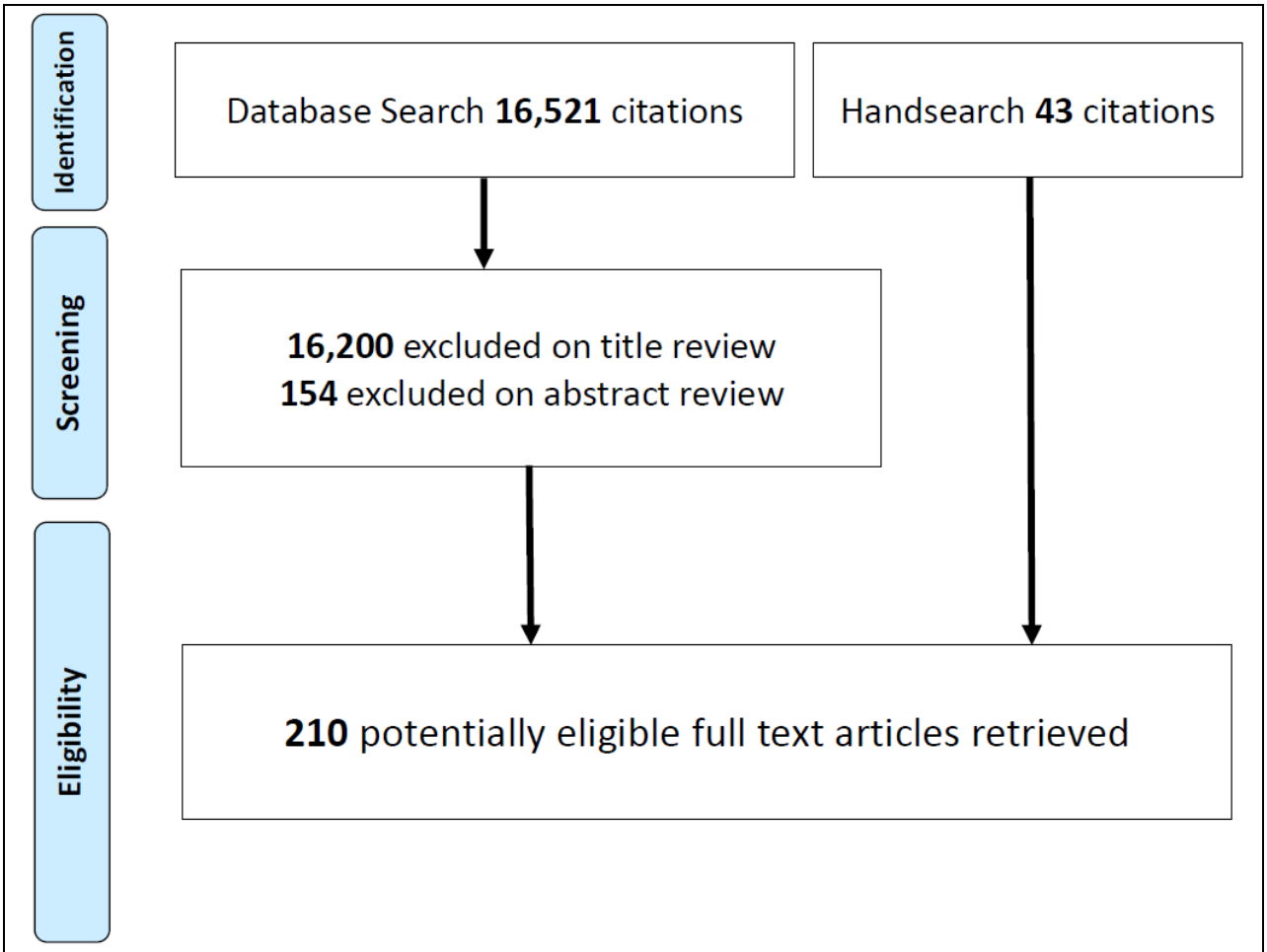


Figure 4.2 Review update search and study selection flowchart

Combined results across search updates for all included procedures.

Table 4.3 Review update study selection process

Procedure	Database	Citations*	Abstracts†	Full texts‡	Hand-search§
Appendicectomy	Cochrane	84			
	MEDLINE	20			
	EMBASE	382			
	Total#	486	18	6	6
Cholecystectomy	Cochrane	1503			
	MEDLINE	2087			
	EMBASE	1260			
	Total#	4670	78	49	4
Colonic resection	Cochrane	122			
	MEDLINE	185			
	EMBASE	224			
	Total#	504	62	24	3
Donor nephrectomy	Cochrane	8			
	MEDLINE	61			
	EMBASE	71			
	Total#	136	0	0	0
Fundoplication	Cochrane	29			
	MEDLINE	67			
	EMBASE	36			
	Total#	132	13	2	4
Gastric bypass	Cochrane	1642			
	MEDLINE	1144			
	EMBASE	2839			
	Total#	5426	22	3	0

Table 4.3 continued

Procedure	Database	Citations*	Abstracts†	Full texts‡	Hand-search§
Inguinal hernia	Cochrane	195			
	MEDLINE	742			
	EMBASE	1158			
	Total#	2034	79	59	22
Rectal resection	Cochrane	560			
	MEDLINE	110			
	EMBASE	1025			
	Total#	1666	47	23	4
Rectopexy	Cochrane	5			
	MEDLINE	520			
	EMBASE	1001			
	Total#	1467	2	1	0

*Number of citation returns per database searched using the search strategy and search start date listed in Table 4.2. This includes duplicate citations. †Number of abstracts selected from the title search. ‡Number of full texts selected from abstract review. §Number of articles identified through a hand-search of additional systematic reviews identified through this review search update process. These were retrieved and subjected to full text review. #Total number of citation returns from all three databases for each procedure's review search update. This total excludes duplicate citations from individual databases, so is usually a smaller number than the sum total of results from the databases.

Retrieval of eligible trials

A combined total of 596 full text articles were assessed at this final stage of the search process for eligibility. Flowcharts summarising the exclusions and final number of included trials per procedure are presented in Figures 4.3 – 4.11. Three hundred and forty eight eligible papers were identified, reporting on a total of 318 RCTs (Appendix D3). RCTs comparing a laparoscopic and open approach for four procedures (appendicectomy, cholecystectomy, colonic resection and inguinal hernia) constituted over 85% of the included studies. There were only two eligible studies assessing rectal rectopexy, meaning that there were insufficient data to include this procedure in subsequent analysis.

Table 4.4 lists the number of RCTs with each bias-minimisation measure included in every outcome analysis per procedure. Over 12% of the included studies were blinded according to the pre-specified definition in this study, with the proportion of blinded RCTs per procedure ranging from 6% to 50%. Most studies did not continue blinding beyond patient discharge. Only one study (Solomon et al., 2002) reported blinding of data analysts, but as there were insufficient other data for this procedure (rectal rectopexy) analysis of this bias-minimisation measure was not possible.

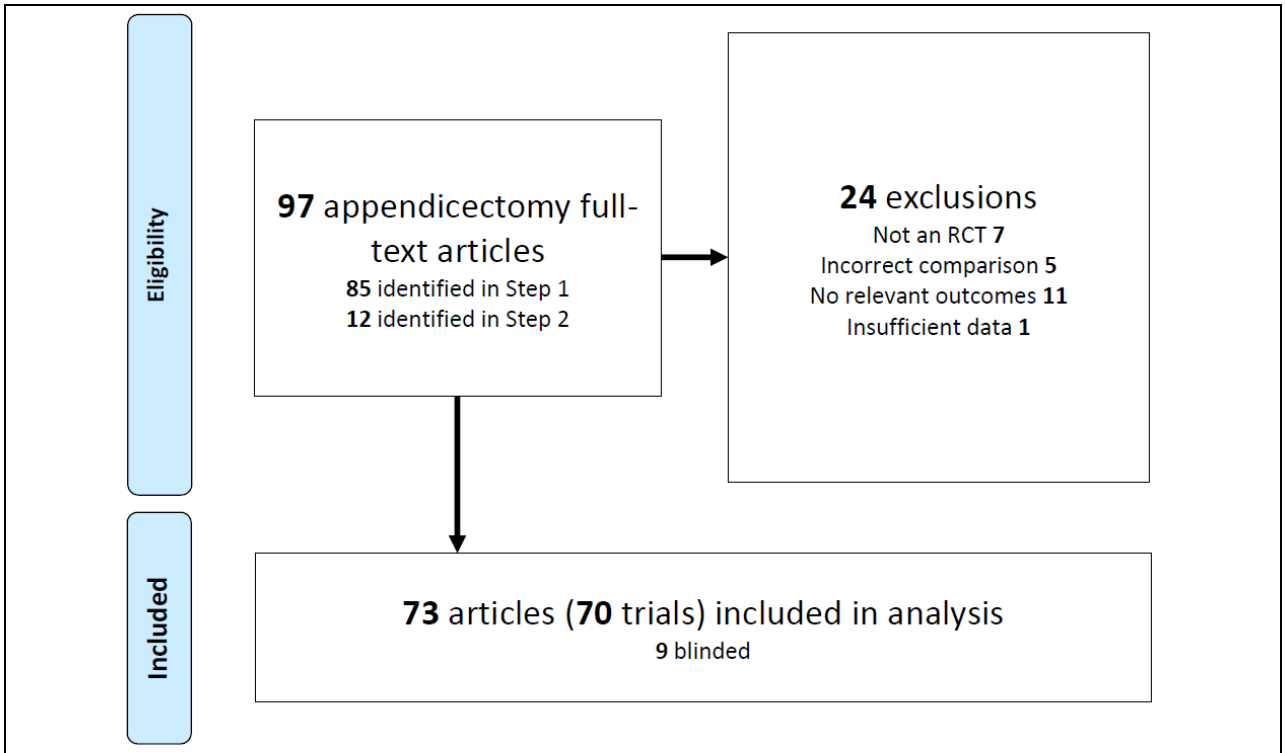


Figure 4.3 Appendicectomy eligible trial selection

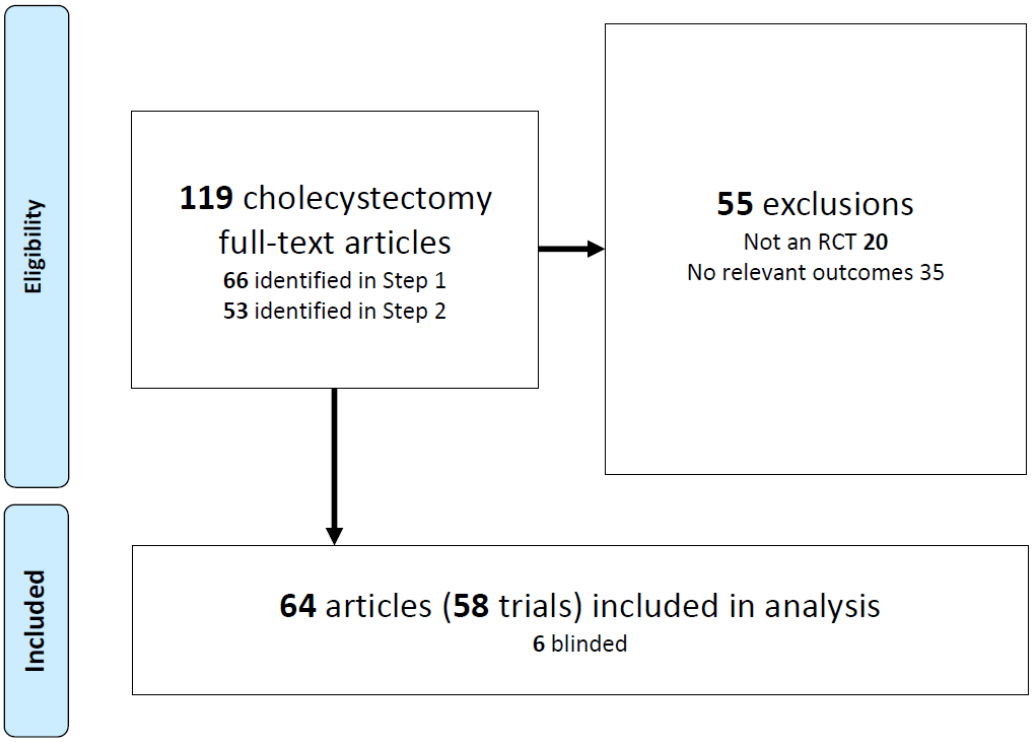


Figure 4.4 Cholecystectomy eligible trial selection

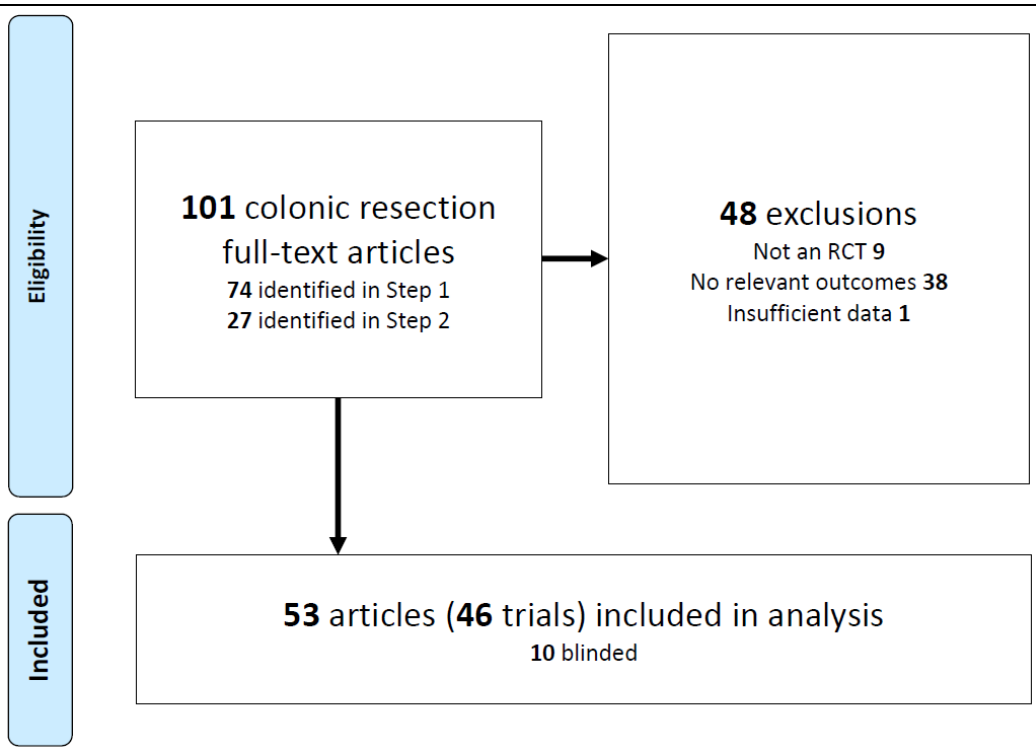


Figure 4.5 Colonic resection eligible trial selection

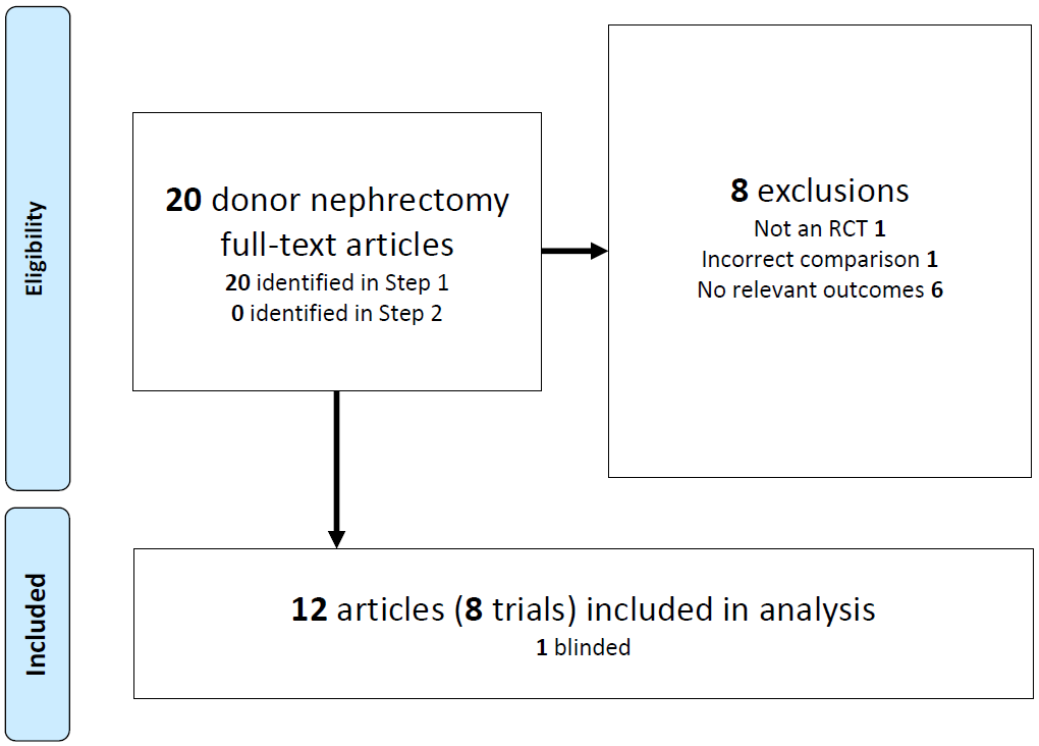


Figure 4.6 Donor nephrectomy eligible trial selection

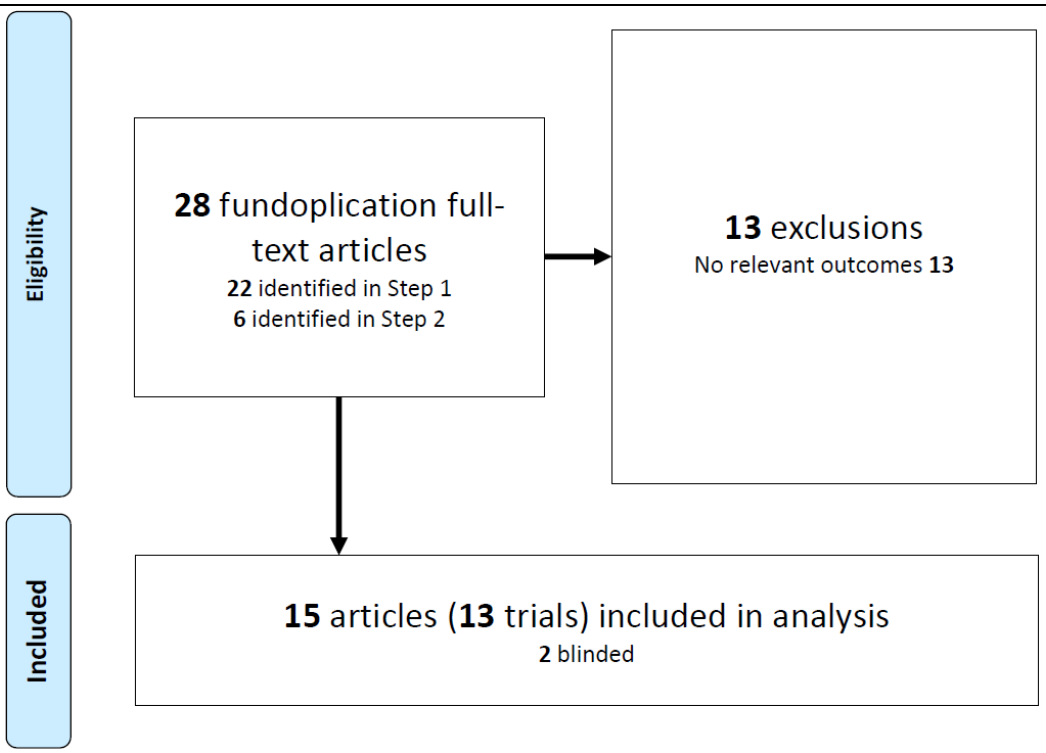


Figure 4.7 Fundoplication eligible trial selection

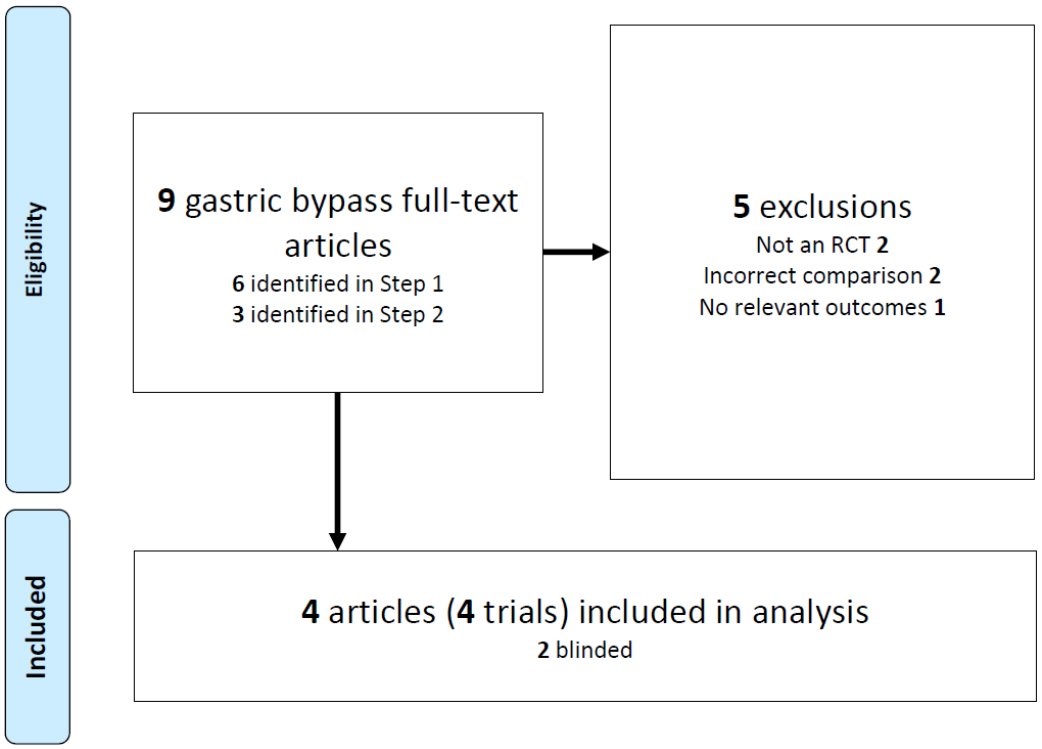


Figure 4.8 Gastric bypass eligible trial selection

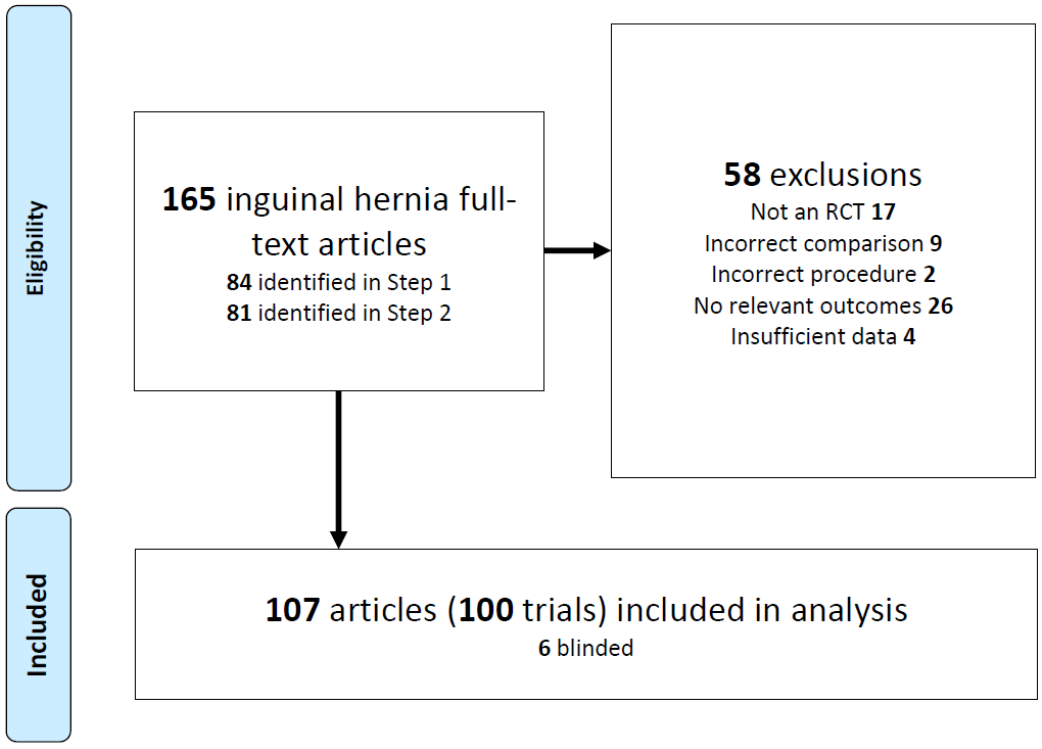


Figure 4.9 Inguinal hernia eligible trial selection

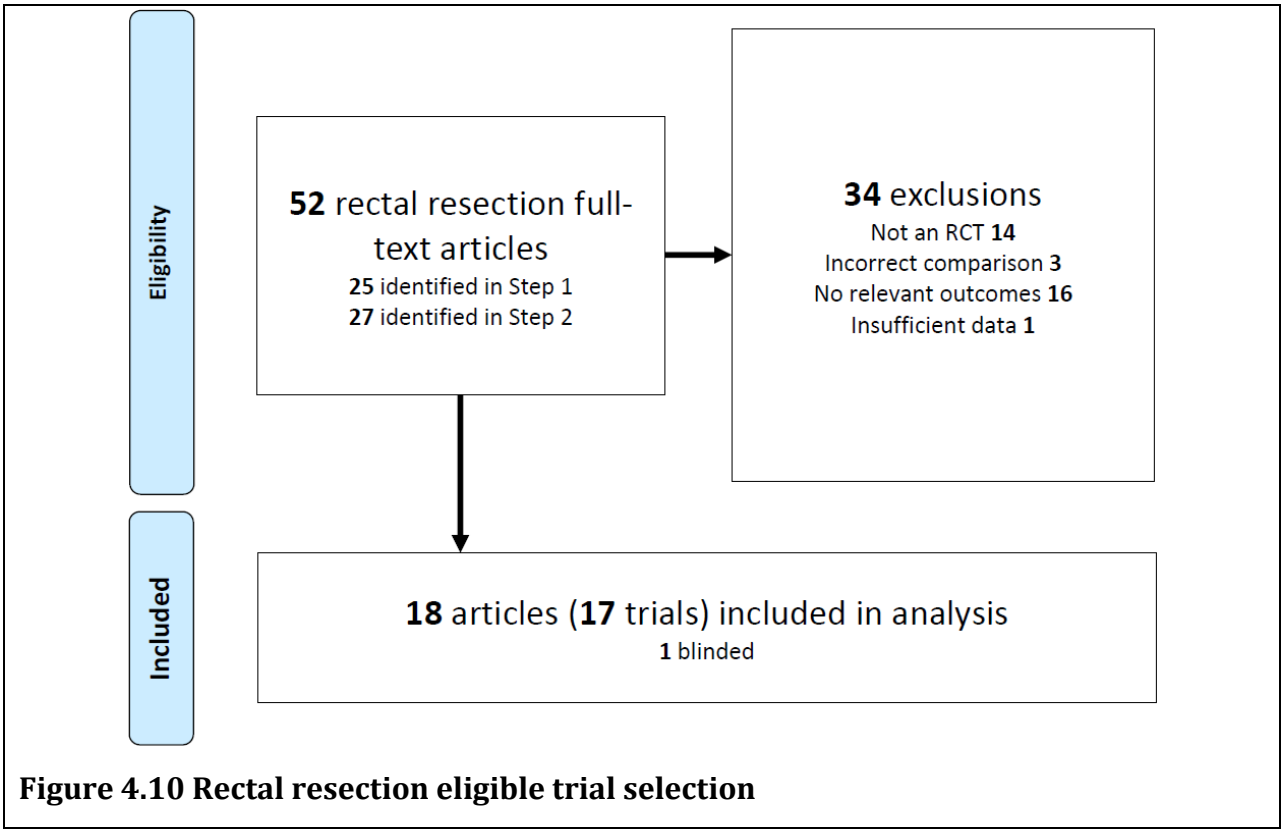


Figure 4.10 Rectal resection eligible trial selection

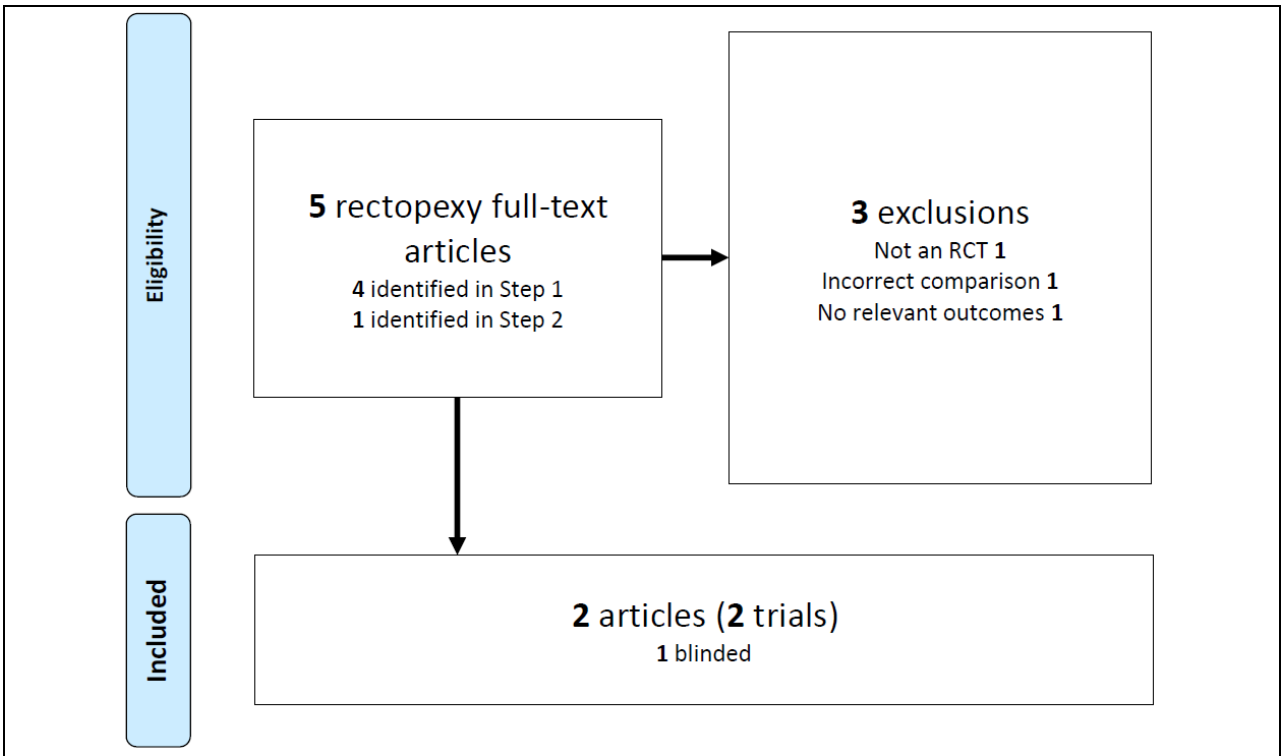


Figure 4.11 Rectopexy eligible trial selection

The eligible rectopexy RCTs could not be included in subsequent analyses as there were insufficient trials for meta-regression for this procedure.

Table 4.4 Included trials with bias-minimisation measures

		Number of included trials with bias-minimisation measure†‡					
Outcome	**Procedure***	**Blinded patients**	**Blinded healthcare staff**	**Blinded data collectors**	**Blinded outcome assessors**	**Random sequence generation§**	**Allocation concealment**
Length of stay	Appendicectomy	7	7	6	4	35	7
	Cholecystectomy	6	6	4	4	22	4
	Colonic resection	7	6	8	3	29	15
	Donor nephrectomy	1	1	-	-	3	2
	Fundoplication	2	2	2	1	4	2
	Gastric bypass	2	2	-	-	-	1
	Inguinal hernia	3	2	2	-	42	10
	Rectal resection	-	-	-	-	10	7
Complications	Appendicectomy	6	6	5	3	36	7
	Cholecystectomy	5	5	4	3	24	2
	Colonic resection	7	6	8	3	29	16
	Donor nephrectomy	1	1	-	-	3	2
	Fundoplication	2	2	2	1	3	2
	Gastric bypass	2	2	-	-	-	1
	Inguinal hernia	4	3	3	1	55	14
	Rectal resection	-	-	-	1	12	7

Table 4.4 continued

		Number of included studies with bias-minimisation measure†‡					
Outcome	**Procedure***	**Blinded patients**	**Blinded healthcare staff**	**Blinded data collectors**	**Blinded outcome assessors**	**Random sequence generation§**	**Allocation concealment**
Time to recovery	Appendicectomy	4	3	4	3	21	4
	Cholecystectomy	4	4	3	2	12	3
	Colonic resection	1	1	2	-	-	1
	Donor nephrectomy	1	1	-	-	2	2
	Fundoplication	1	1	1	1	2	1
	Gastric bypass	2	2	-	-	2	-
	Inguinal hernia	4	3	2	1	45	11
Short-term pain	Appendicectomy	4	4	4	2	13	3
	Cholecystectomy	3	3	1	1	11	1
	Colonic resection	4	3	6	1	16	6
	Donor nephrectomy	1	1	-	-	3	2
	Inguinal hernia	3	3	3	1	38	7
	Rectal resection	-	-	-	-	3	3

Table 4.4 continued

		Number of included studies with bias-minimisation measure†‡					
Outcome	**Procedure***	**Blinded patients**	**Blinded healthcare staff**	**Blinded data collectors**	**Blinded outcome assessors**	**Random sequence generation§**	**Allocation concealment**
Long-term pain	Cholecystectomy	1	1	1	-	-	-
	Colonic resection	1	1	1	1	5	3
	Donor nephrectomy	1	1	-	-	2	1
	Inguinal hernia	-	-	-	-	11	5
Time to flatus	Cholecystectomy	-	-	-	-	2	1
	Colonic resection	1	2	2	1	12	7
	Rectal resection	-	-	-	1	8	6
Time to bowel motion	Appendicectomy	-	-	-	-	1	-
	Cholecystectomy	-	-	-	-	1	-
	Colonic resection	3	3	2	2	13	6
	Rectal resection	-	-	-	1	8	8

*There were insufficient rectopexy trials to include this procedure in any analysis, so it is not listed here. Procedures with reported data for an outcome but where these were insufficient for inclusion in the relevant analysis are not listed under that outcome. †Only one trial (assessing rectopexy) reported blinding of data analysts (which could not be analysed due to insufficient data for that procedure), so assessment of this bias-minimisation measure was not possible. ‡A dash (-) indicates that there were insufficient data to include that procedure in the analysis for that bias-minimisation measure and outcome. For a procedure to be included at least one of the RCTs reporting that outcome had to report use of the bias-minimisation measure in question, with sufficient data available from other trials (which did not use that measure) assessing the same outcome for that procedure. §As non-randomised studies were not included, this domain assessed whether generation of the randomisation sequence was correctly performed according to the Cochrane Risk of Bias tool's criteria, rather than the presence or absence of randomisation.

4.4.2 Length of stay

A total of 254 RCTs reported this outcome, of which two investigated rectopexy and were unable to be included in any of the analyses because of insufficient data. Length of stay meta-regression results are shown in Figures 4.12 – 4.18, with a summative analysis of any blinding in Figure 4.16.

Studies that used a blinding measure reported a smaller difference in length of stay between the laparoscopic and open groups compared to those that did not use that blinding measure, and this difference was up to 0.5 SD. The point estimates in each analysis show that this was consistent across the majority of procedures, and the I^2 statistic for most analyses was low, indicating low between-procedure heterogeneity. The summative analysis further demonstrates this with blinded trials reporting a smaller difference of 0.34 SD compared to non-blinded trials.

RCTs judged to have generated an appropriate randomisation sequence also reported a smaller difference in length of stay between the laparoscopic and open groups. However, this difference was not statistically significant and the I^2 statistic for this analysis showed evidence of significant between-procedure heterogeneity. This was largely driven by the result for donor nephrectomy trials, which were a relatively small number (seven). Sensitivity analysis excluding this procedure showed a much smaller I^2 statistic, and a similar overall result. Allocation concealment did not appear to significantly influence the reported difference in length of stay, with an overall DSMD approaching zero.

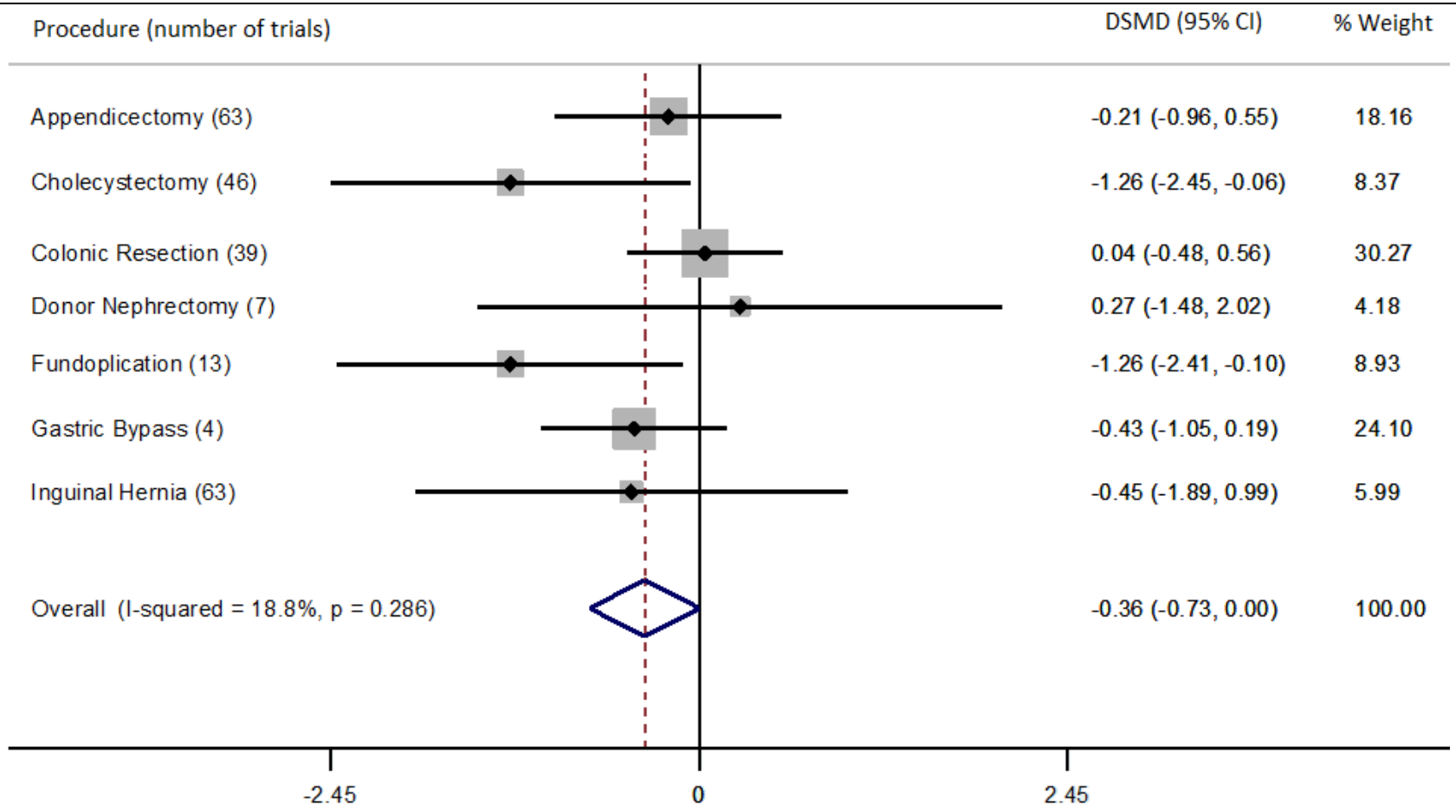


Figure 4.12 Length of stay forest plot – meta-regression of patient blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

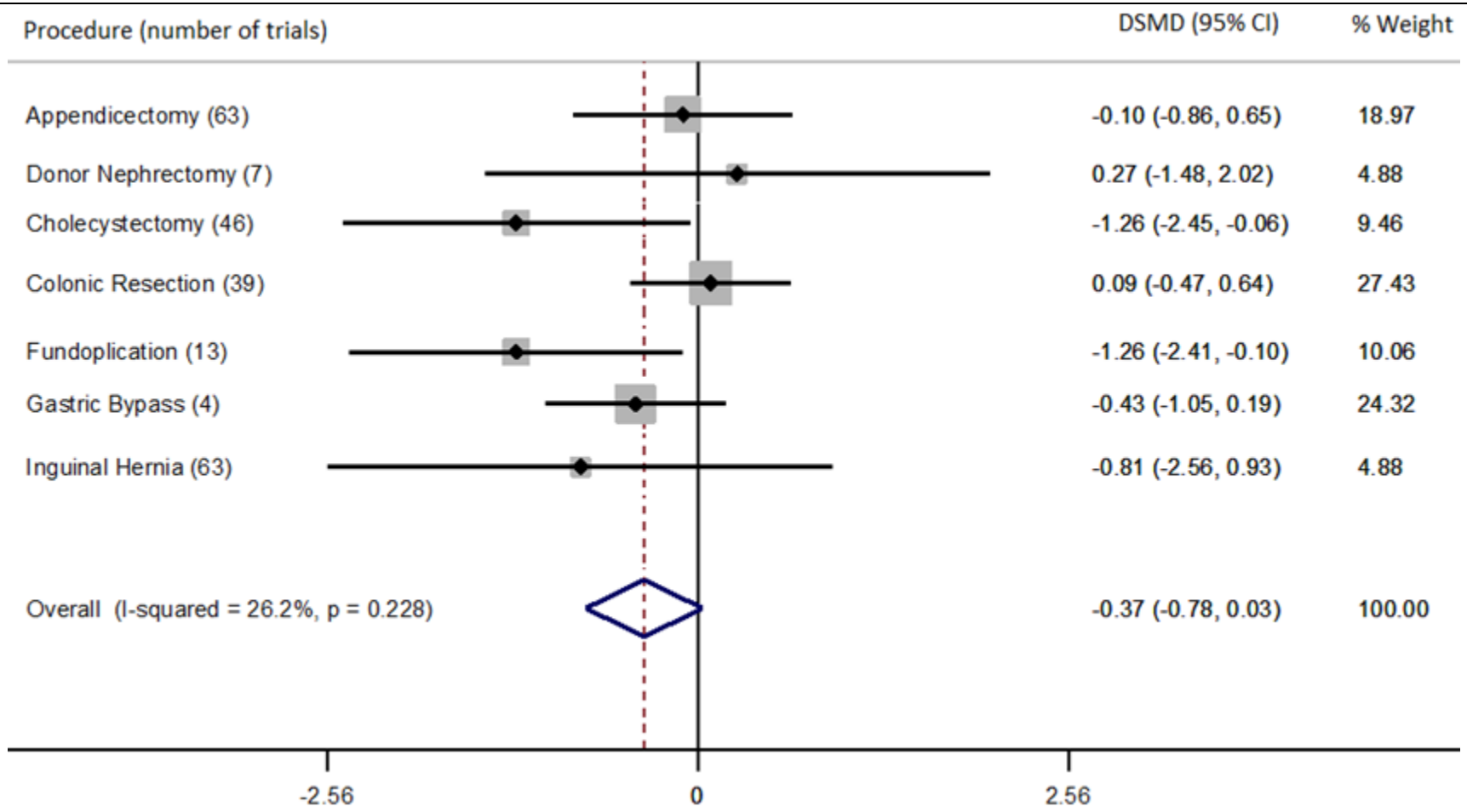


Figure 4.13 Length of stay forest plot – meta-regression of healthcare staff blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

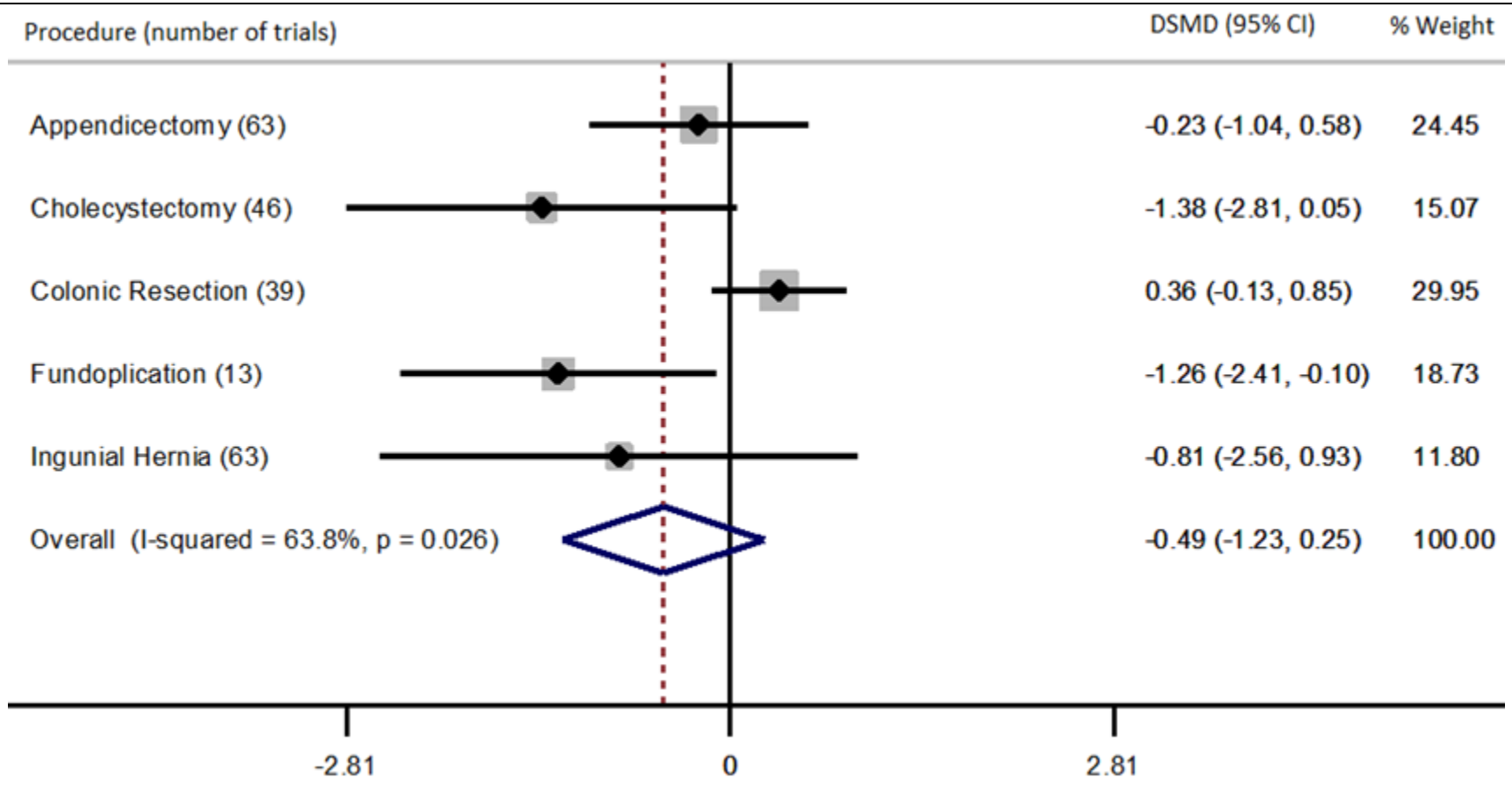


Figure 4.14 Length of stay forest plot – meta-regression of data collector blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

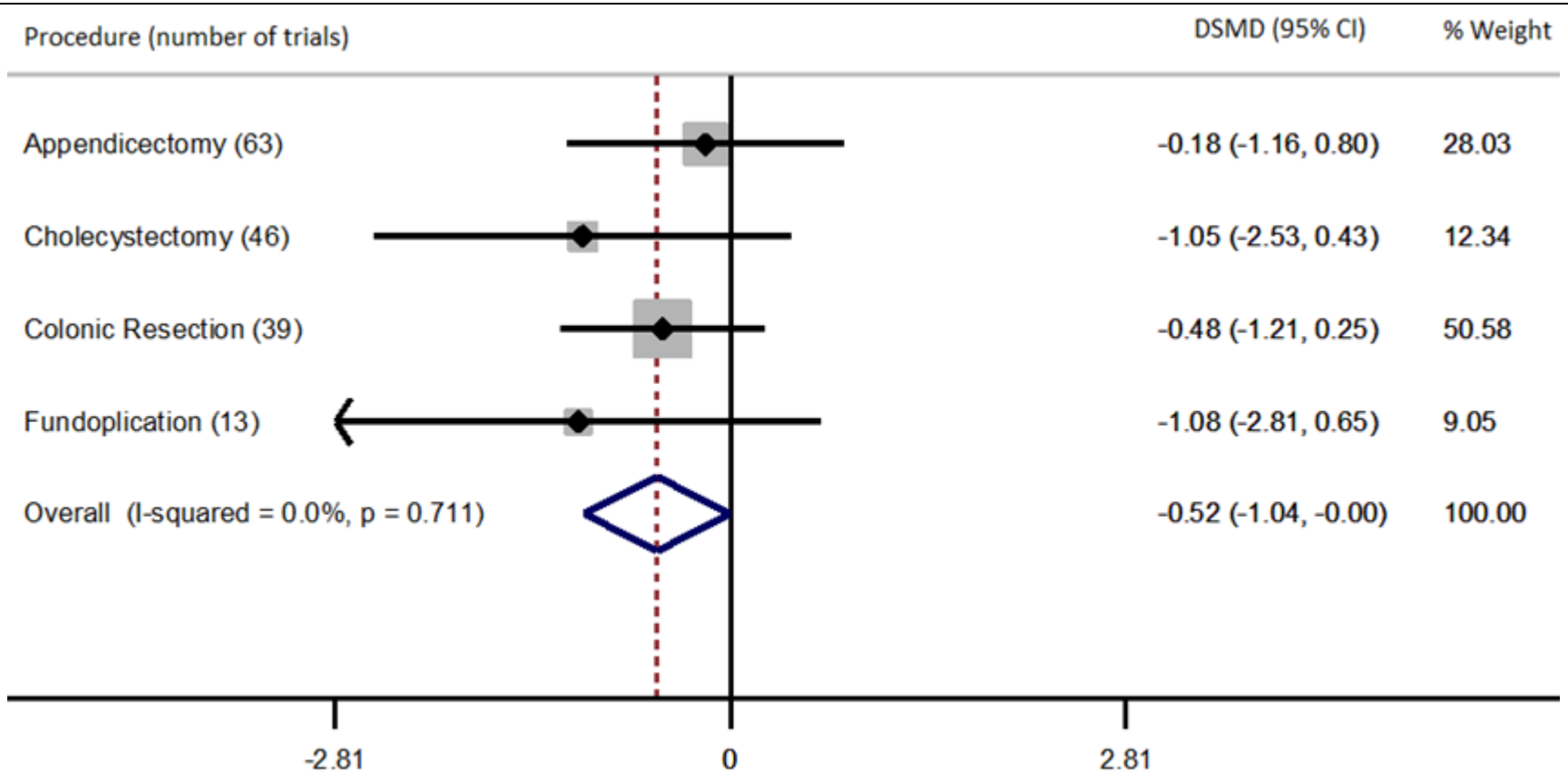


Figure 4.15 Length of stay forest plot – meta-regression of outcome assessor blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

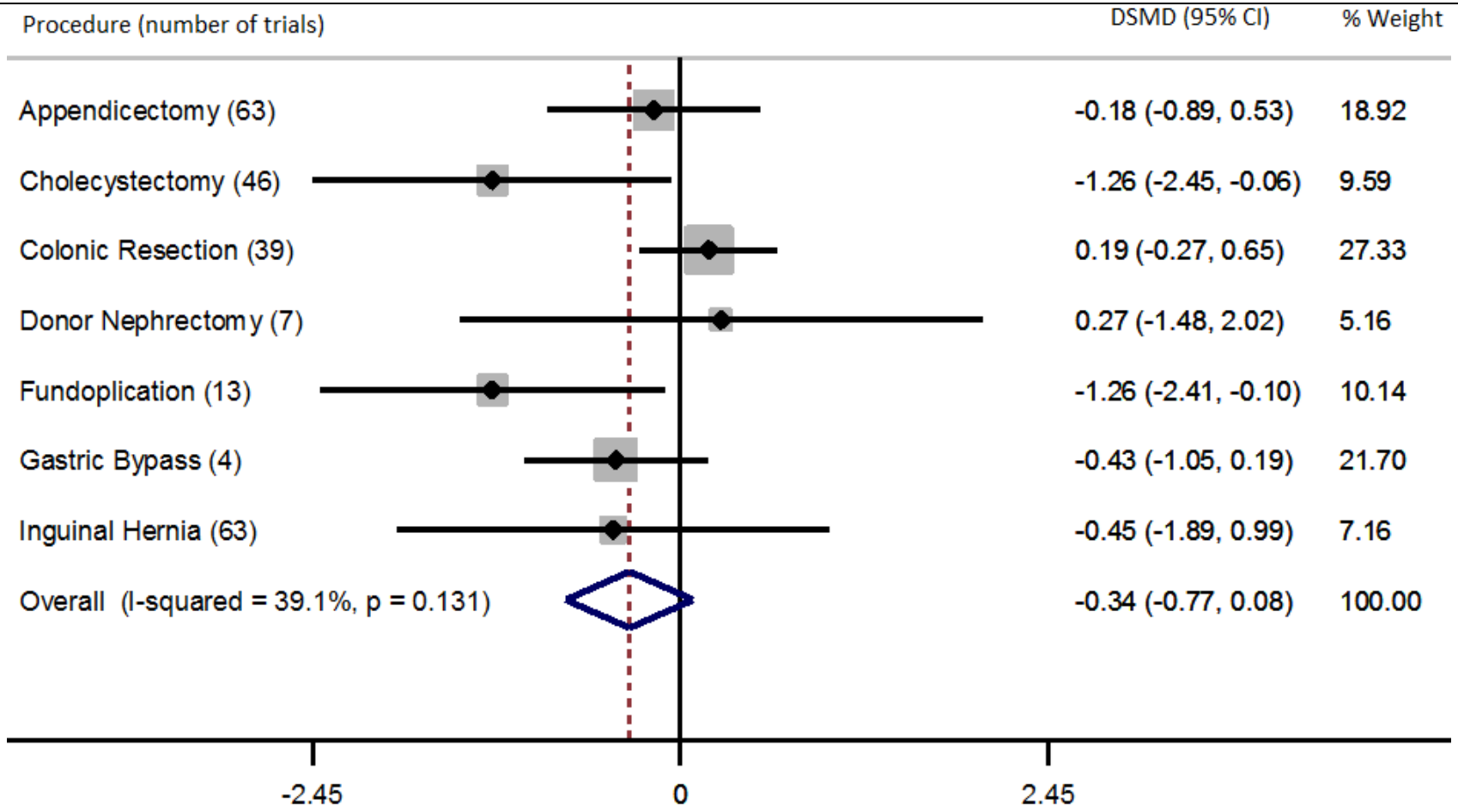


Figure 4.16 Length of stay forest plot – meta-regression of any blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

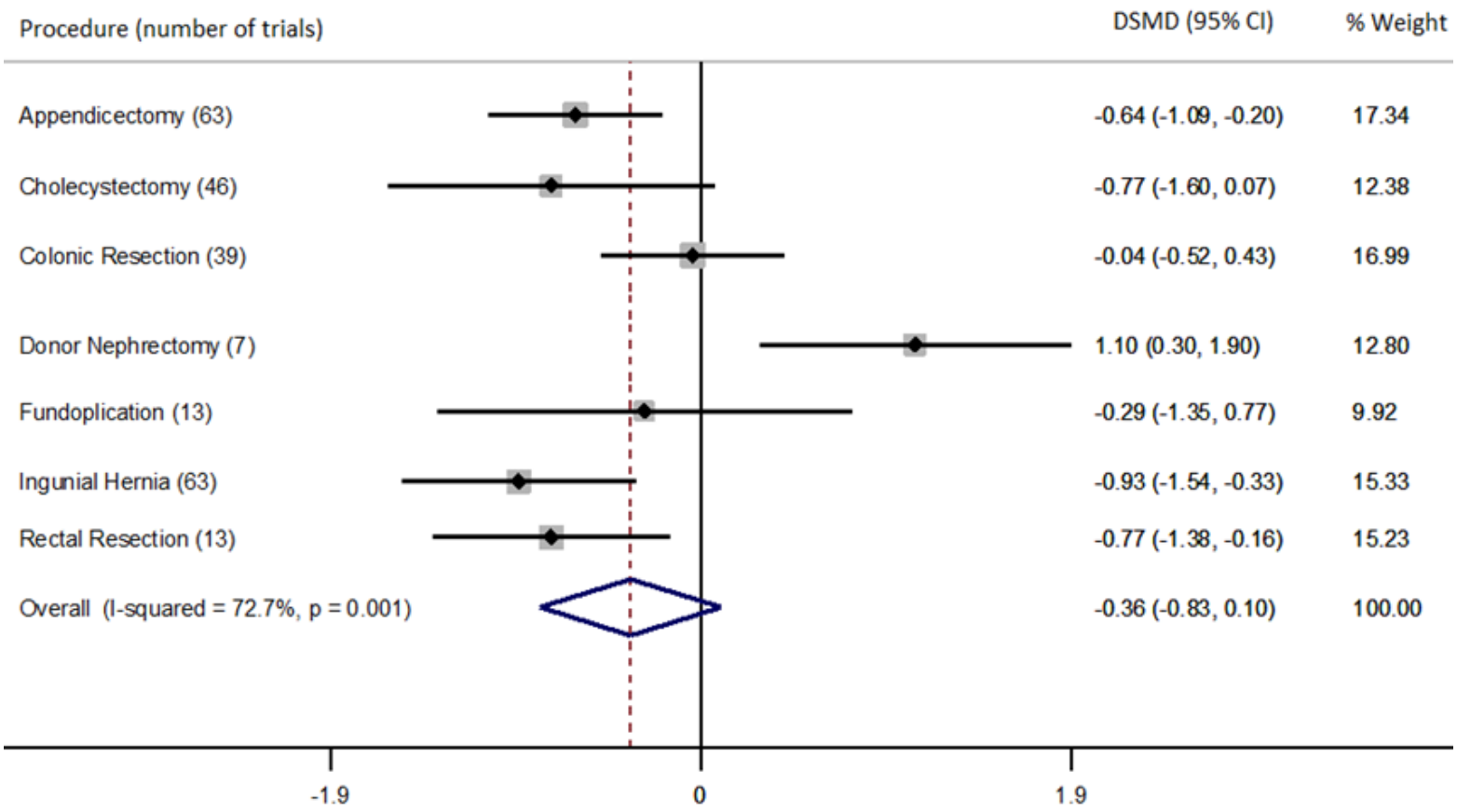


Figure 4.17 Length of stay forest plot – meta-regression of random sequence generation

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

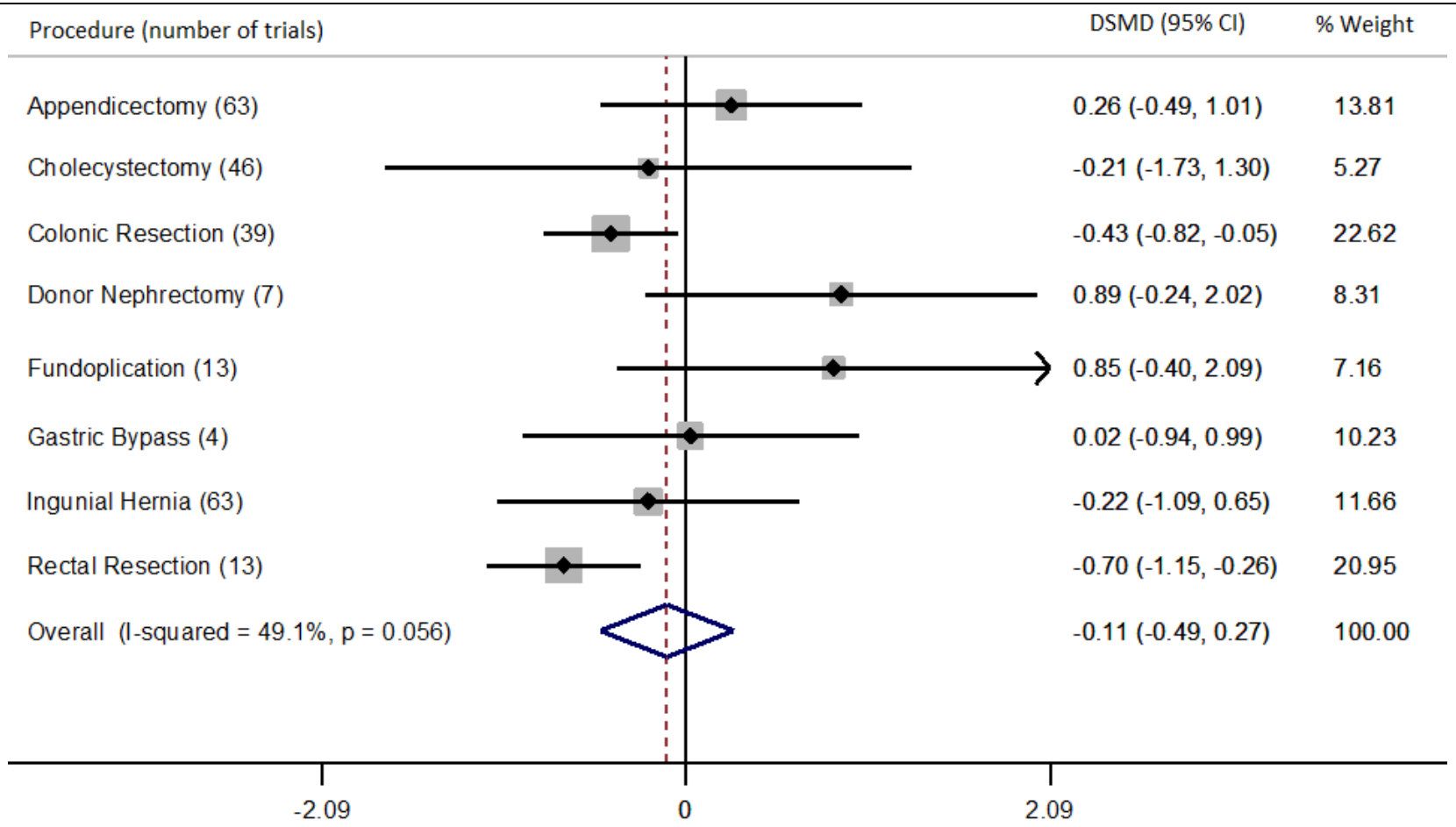


Figure 4.18 Length of stay forest plot – meta-regression of allocation concealment

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

4.4.3 Complications

This was the most commonly reported outcome with data from 281 studies available for analysis, after exclusion of one study investigating rectopexy. Figures 4.19 – 4.25 summarise the meta-regression results for this outcome, and the summary 'any blinding' analysis is shown in Figure 4.23.

Significantly smaller differences in the number of complications between the laparoscopic and open groups were reported by studies where patients and healthcare staff were blinded compared to those where those groups were not. The I^2 statistic for both these analyses was zero, meaning no evidence of between-procedure heterogeneity. For most procedures, smaller differences were also reported by studies where data collectors and outcome assessors were blinded, though fewer data were available for these analyses and the confidence intervals included the null value (ROR = 1). The summative analysis (Figure 4.25) shows a similar result to the individual blinding analyses.

Appropriate generation of a randomisation sequence was also associated with a smaller reported difference in the complication rate between the laparoscopic and open groups, though this was not statistically significant and point estimates for the procedures were variable. The reported difference in complications was not influenced by the presence or absence of allocation concealment.

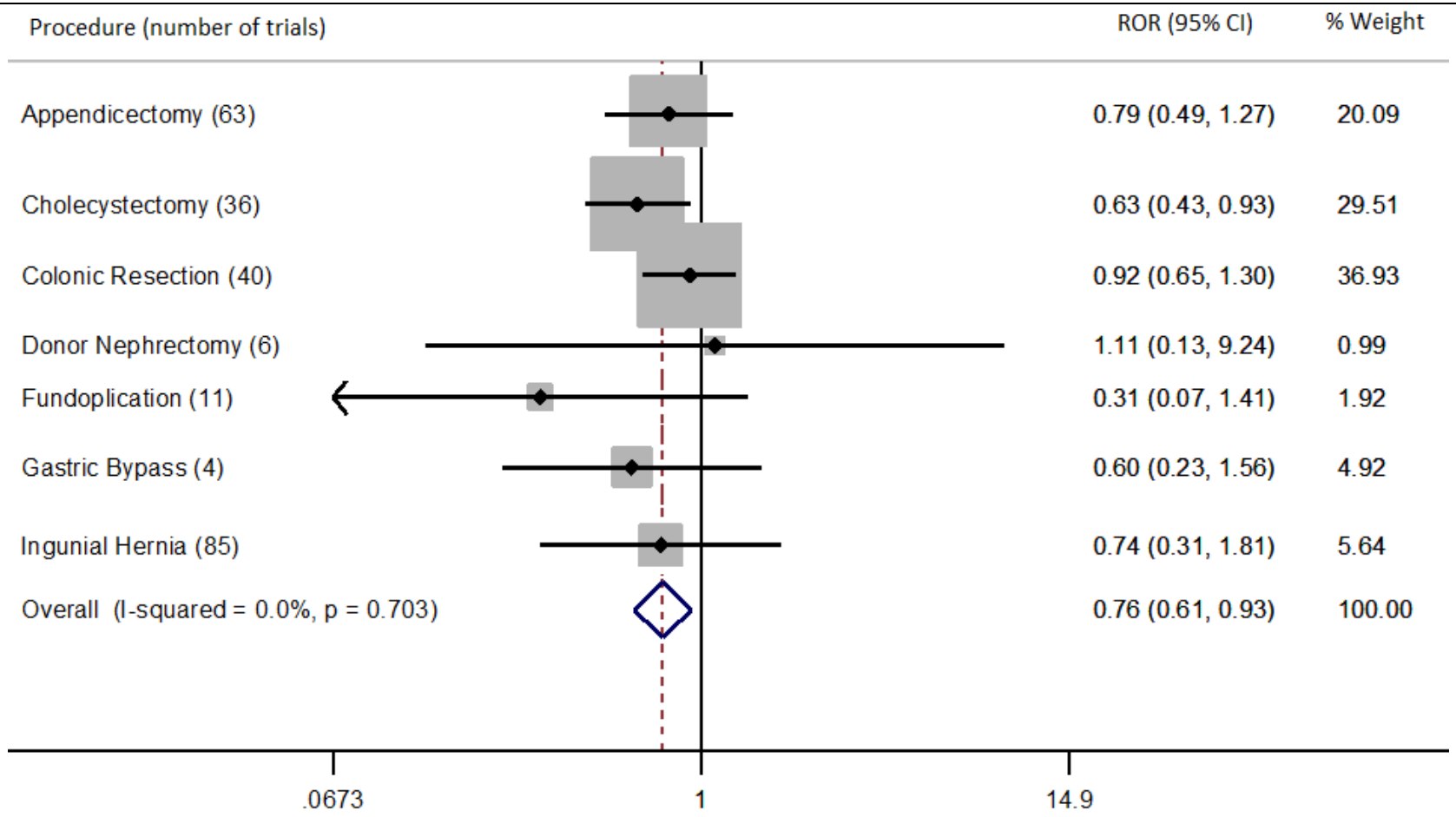


Figure 4.19 Complications forest plot – meta-regression of patient blinding

Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. ROR = Ratio of odds ratios.

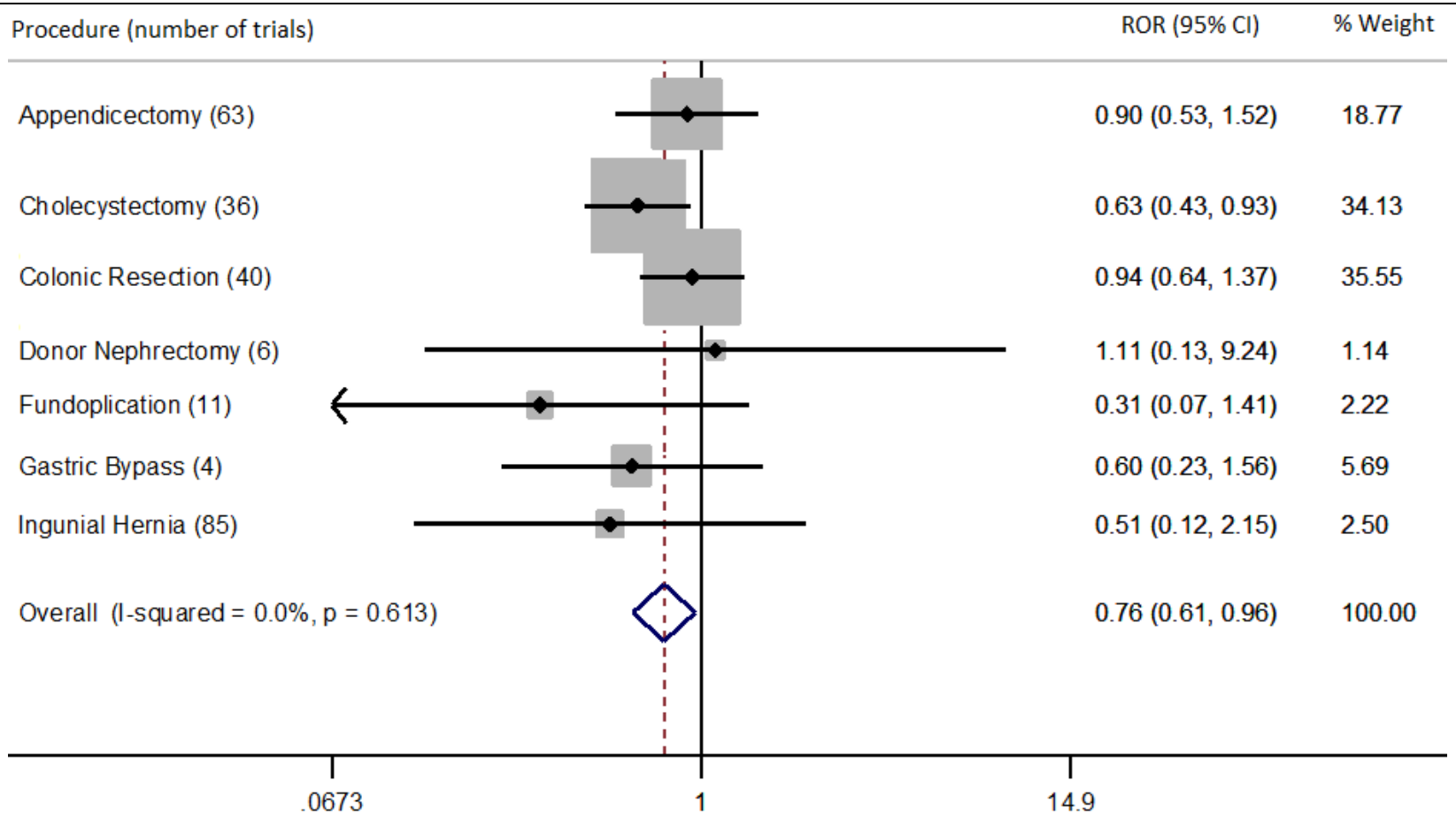


Figure 4.20 Complications forest plot – meta-regression of healthcare staff blinding

Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. ROR = Ratio of odds ratios.

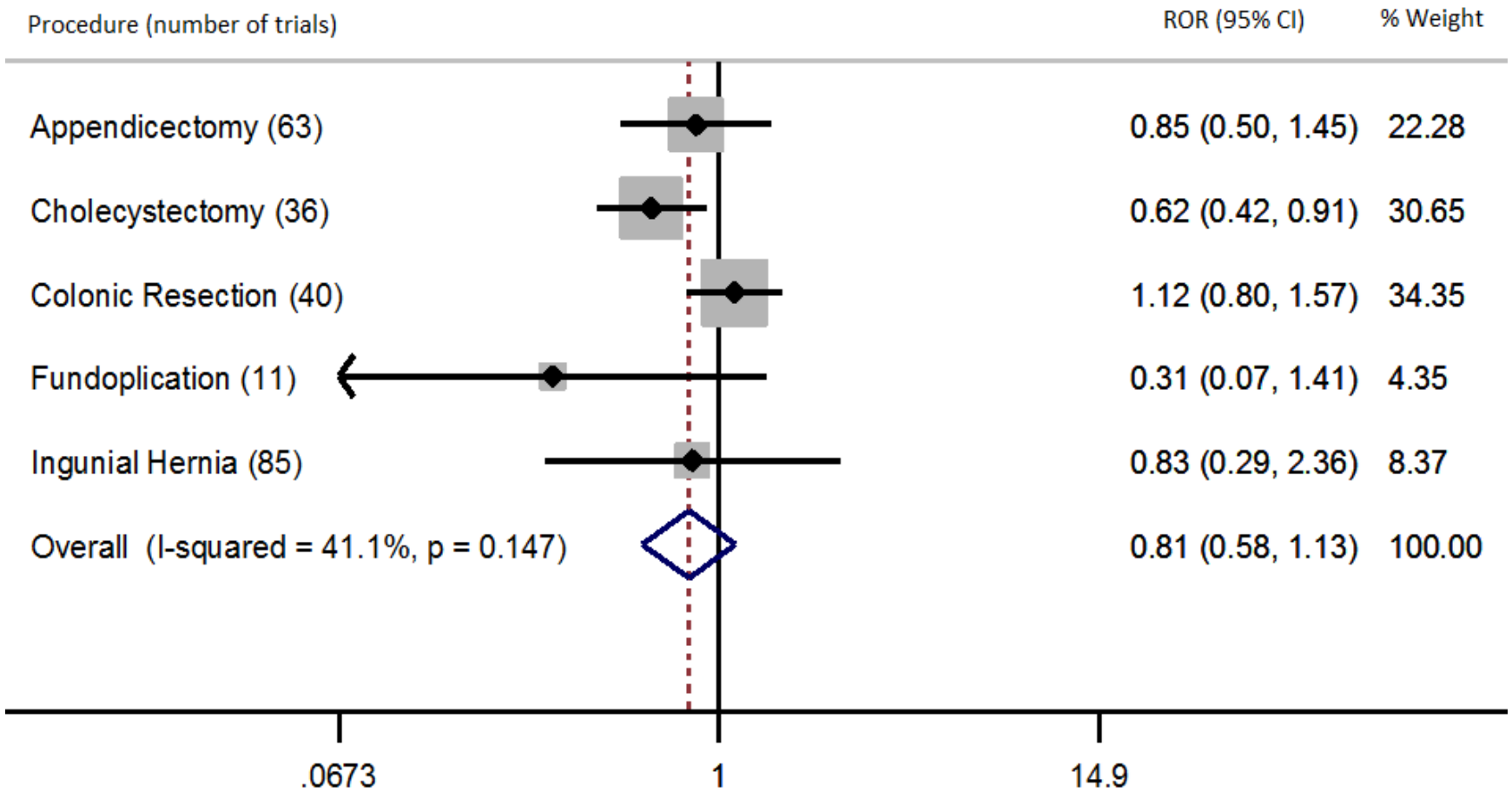


Figure 4.21 Complications forest plot – meta-regression of data collector blinding

Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. ROR = Ratio of odds ratios.

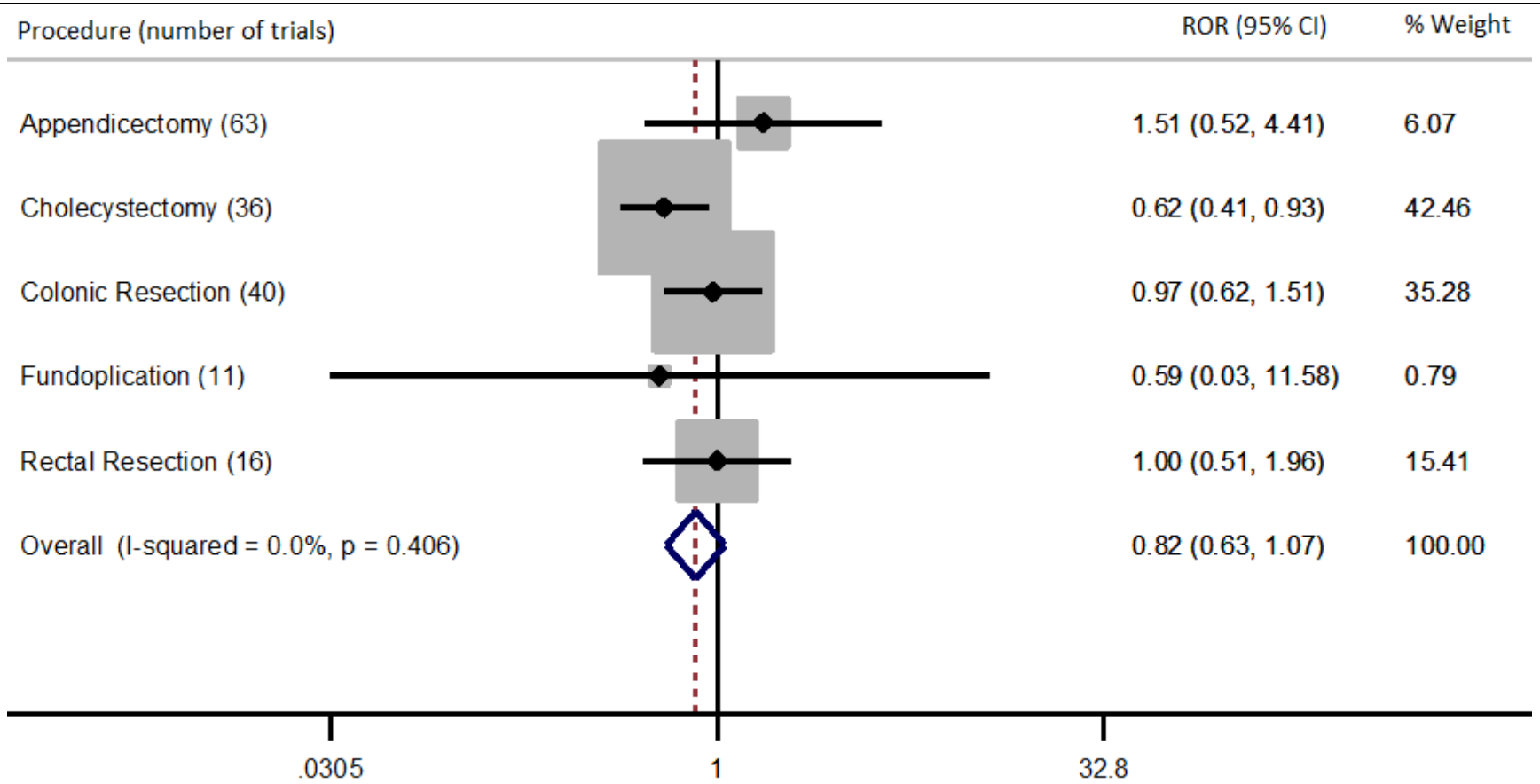


Figure 4.22 Complications forest plot – meta-regression of outcome assessor blinding

Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. ROR = Ratio of odds ratios.

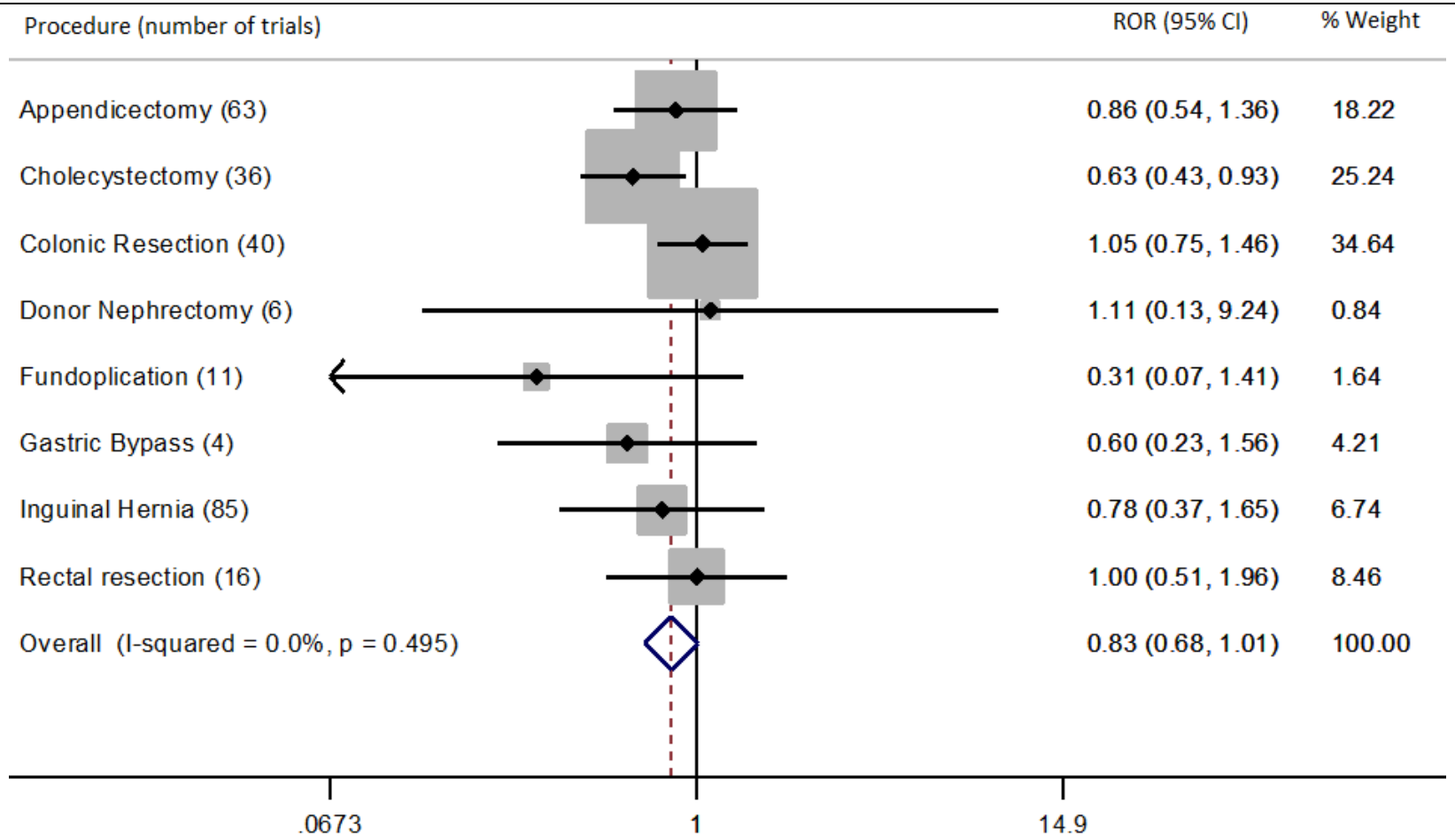


Figure 4.23 Complications forest plot – meta-regression of any blinding

Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. ROR = Ratio of odds ratios.

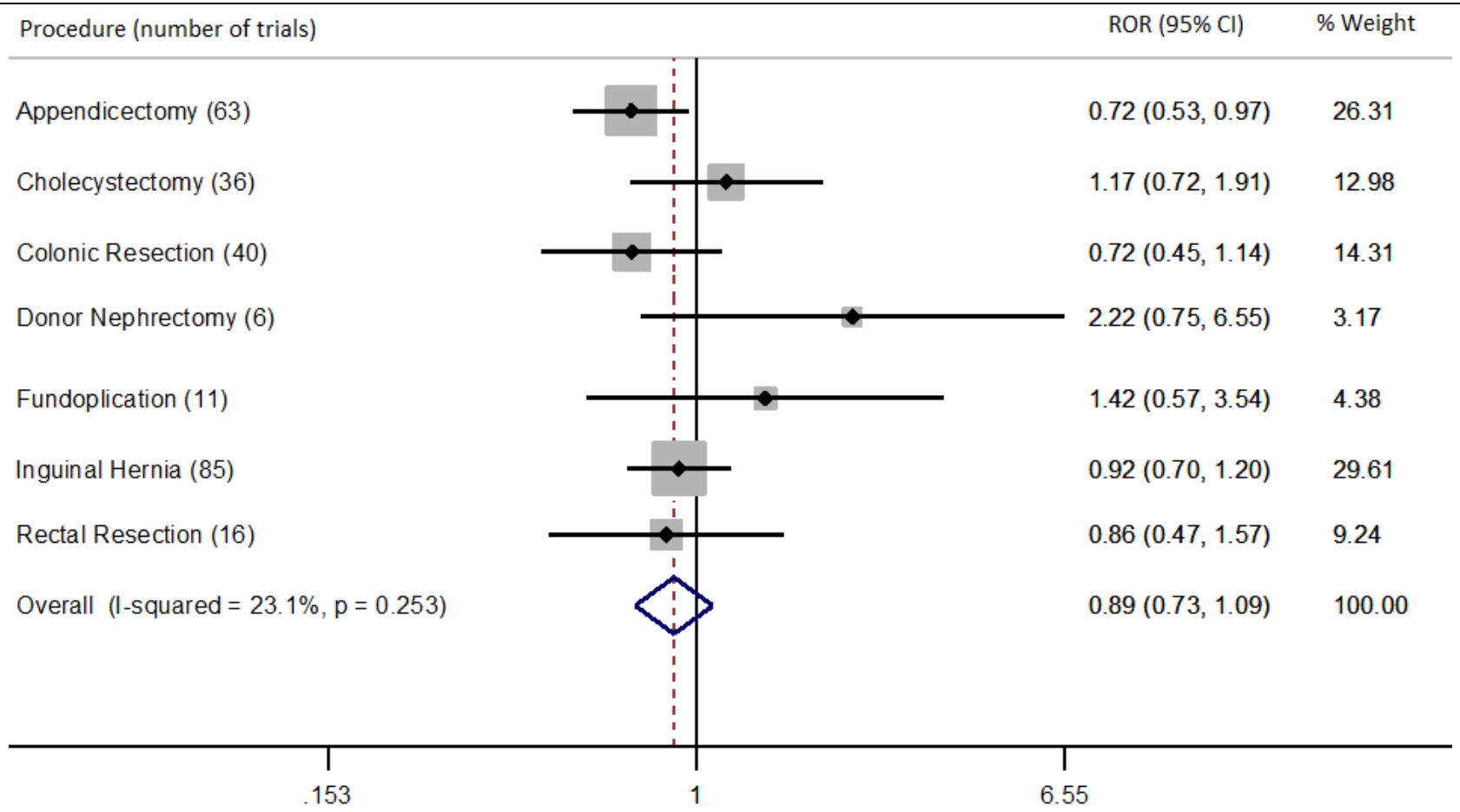


Figure 4.24 Complications forest plot – meta-regression of random sequence generation

Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. ROR = Ratio of odds ratios.

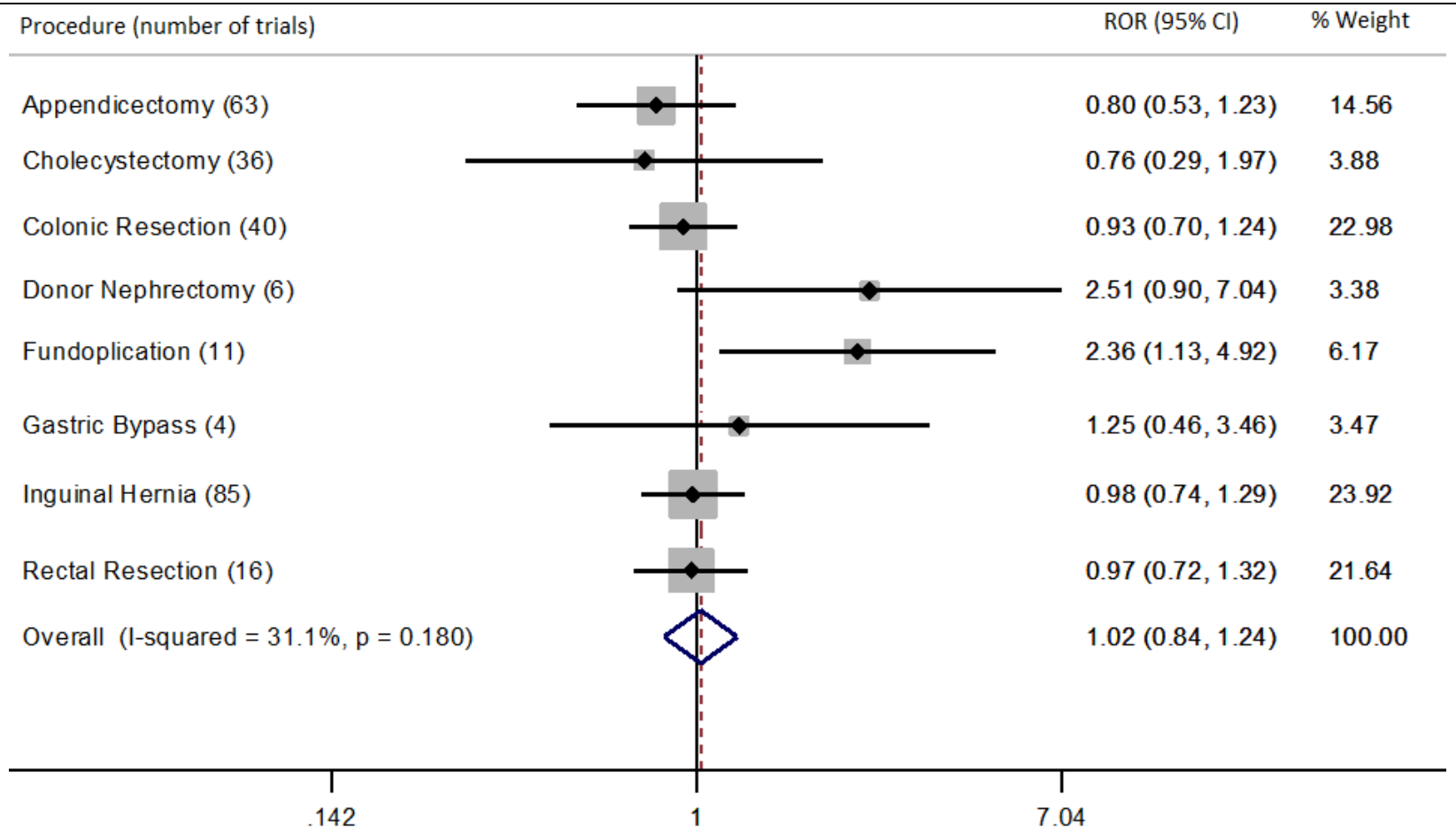


Figure 4.25 Complications forest plot – meta-regression of allocation concealment

Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. ROR = Ratio of odds ratios.

4.4.4 Secondary outcomes

Time to recovery

One hundred and forty one studies reported this outcome, with insufficient data available for rectal resection to enable inclusion in the analyses. Analysis results are summarised in Figures 4.26 – 4.31. None of the blinding groups were still blinded at the time this outcome was attained by patients, so comparisons are between studies where blinding had occurred at the initial stages (e.g. before patient discharge) compared to others where no blinding was attempted during the trial.

A smaller difference in time to recovery between laparoscopic and open groups was reported by studies where any of the blinding measures were undertaken compared to non-blinded RCTs, apart from data collectors. Although the 95% confidence intervals for these analyses included zero, this was partly influenced by the results for colonic resection RCTs, which were only four for this outcome with just one blinded study. Sensitivity analysis excluding this procedure resulted in narrower confidence intervals for the difference between blinded and non-blinded studies.

Both correctly performed random sequence generation and allocation concealment also influenced the reported results of trials, with studies where those measures were used reporting a smaller difference in time to recovery across most procedures. Confidence intervals for both analyses included zero however, and the influence of allocation concealment was relatively small (0.2 SD).

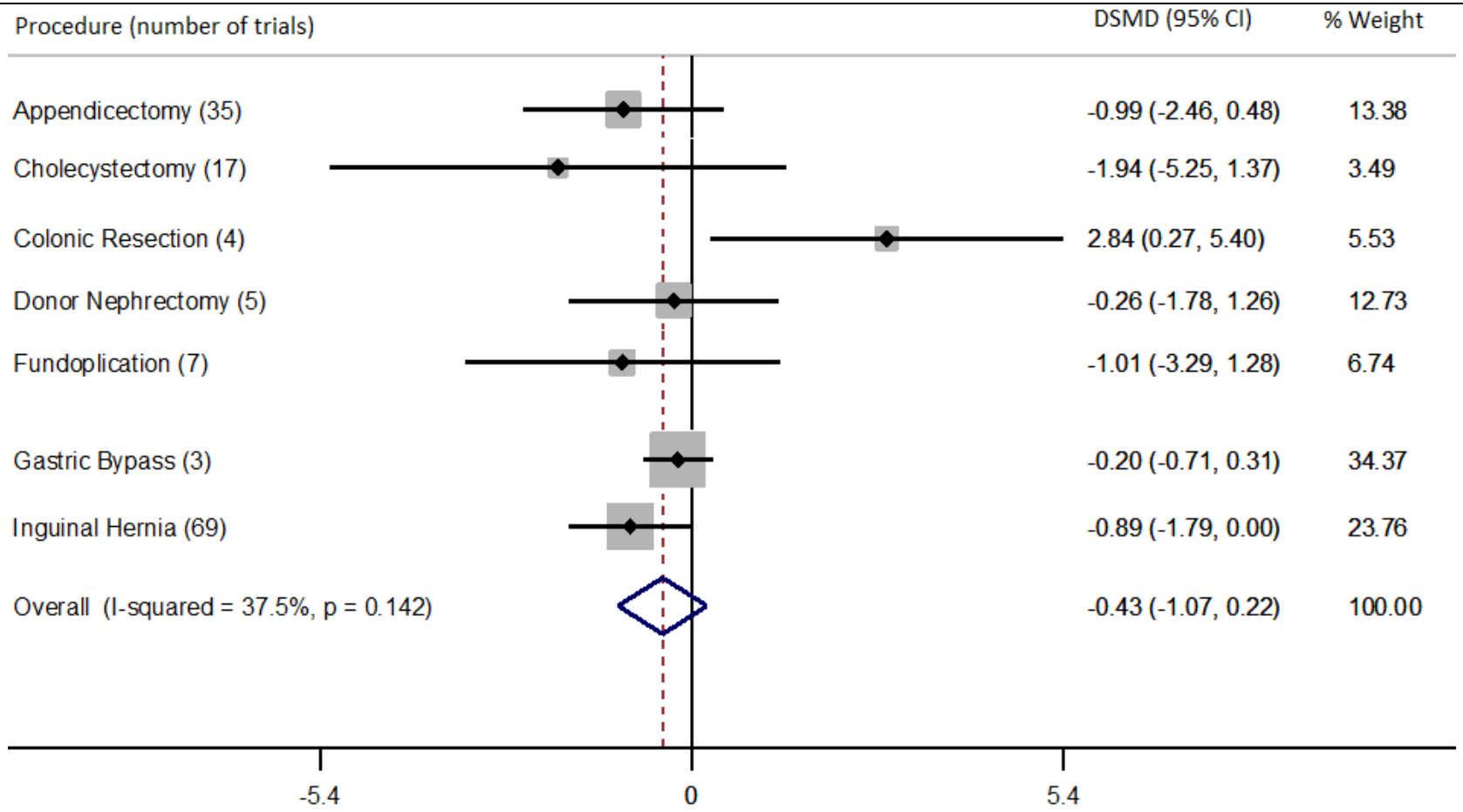


Figure 4.26 Time to recovery forest plot – meta-regression of patient blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

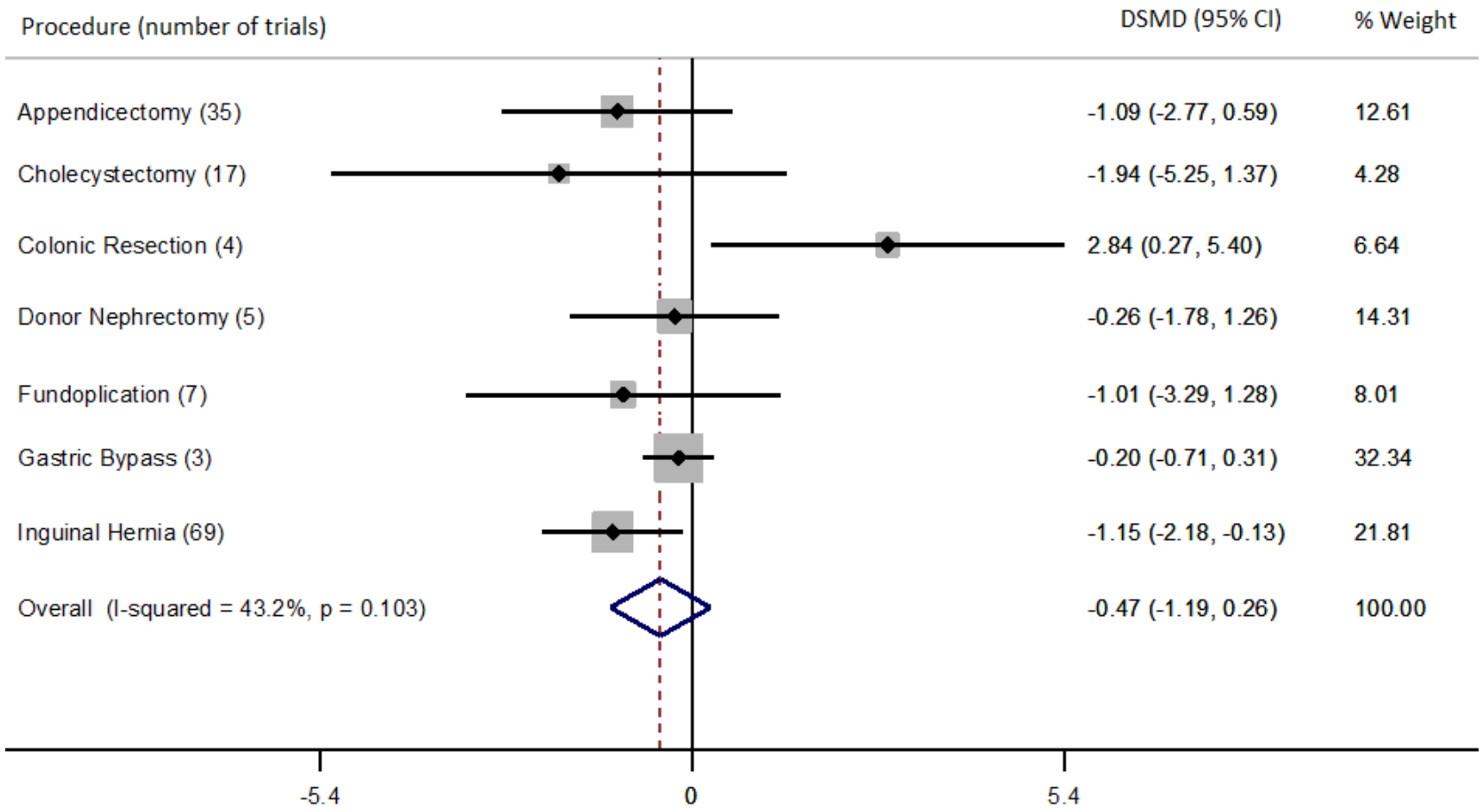


Figure 4.27 Time to recovery forest plot – meta-regression of healthcare staff blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

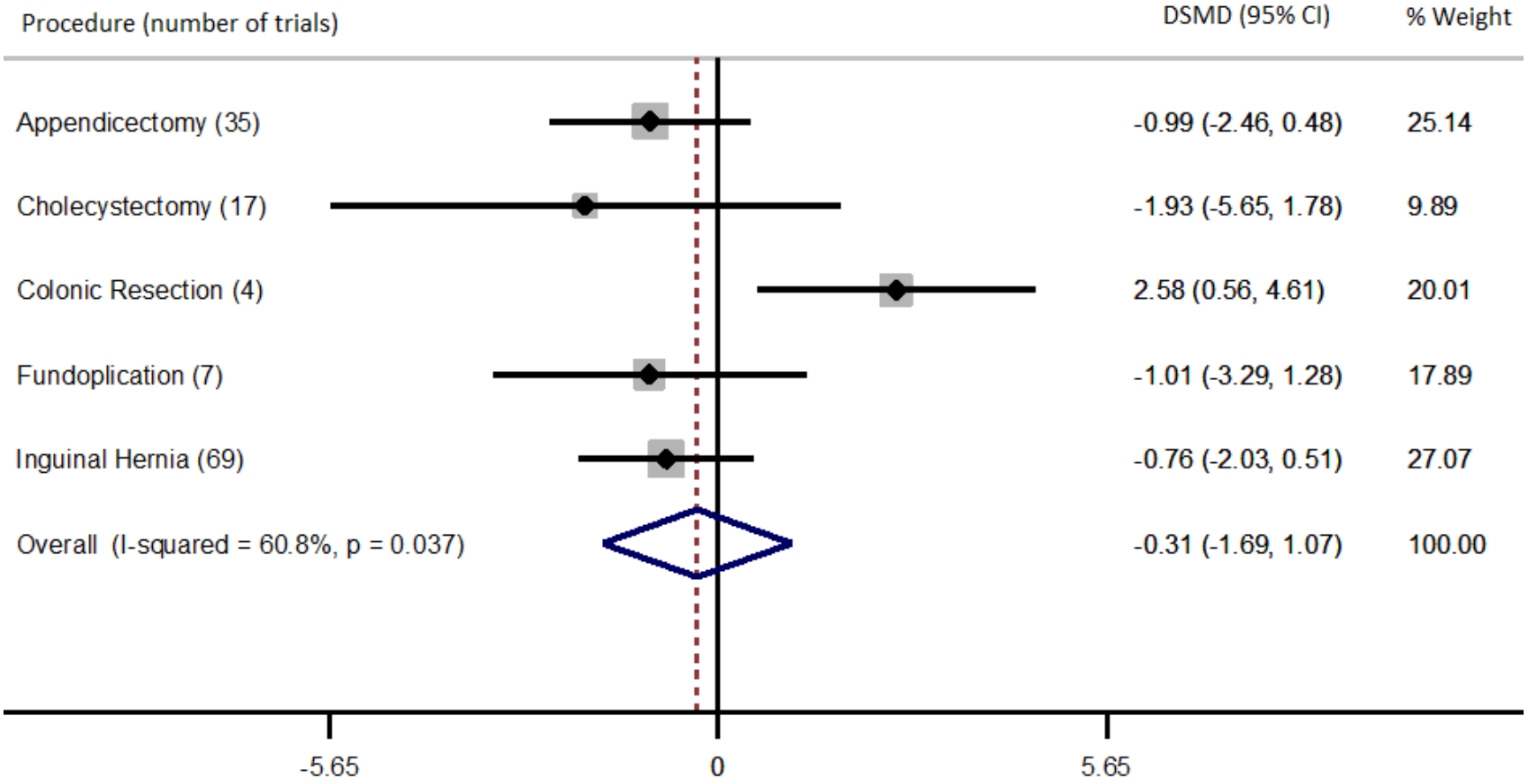


Figure 4.28 Time to recovery forest plot – meta-regression of data collector blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

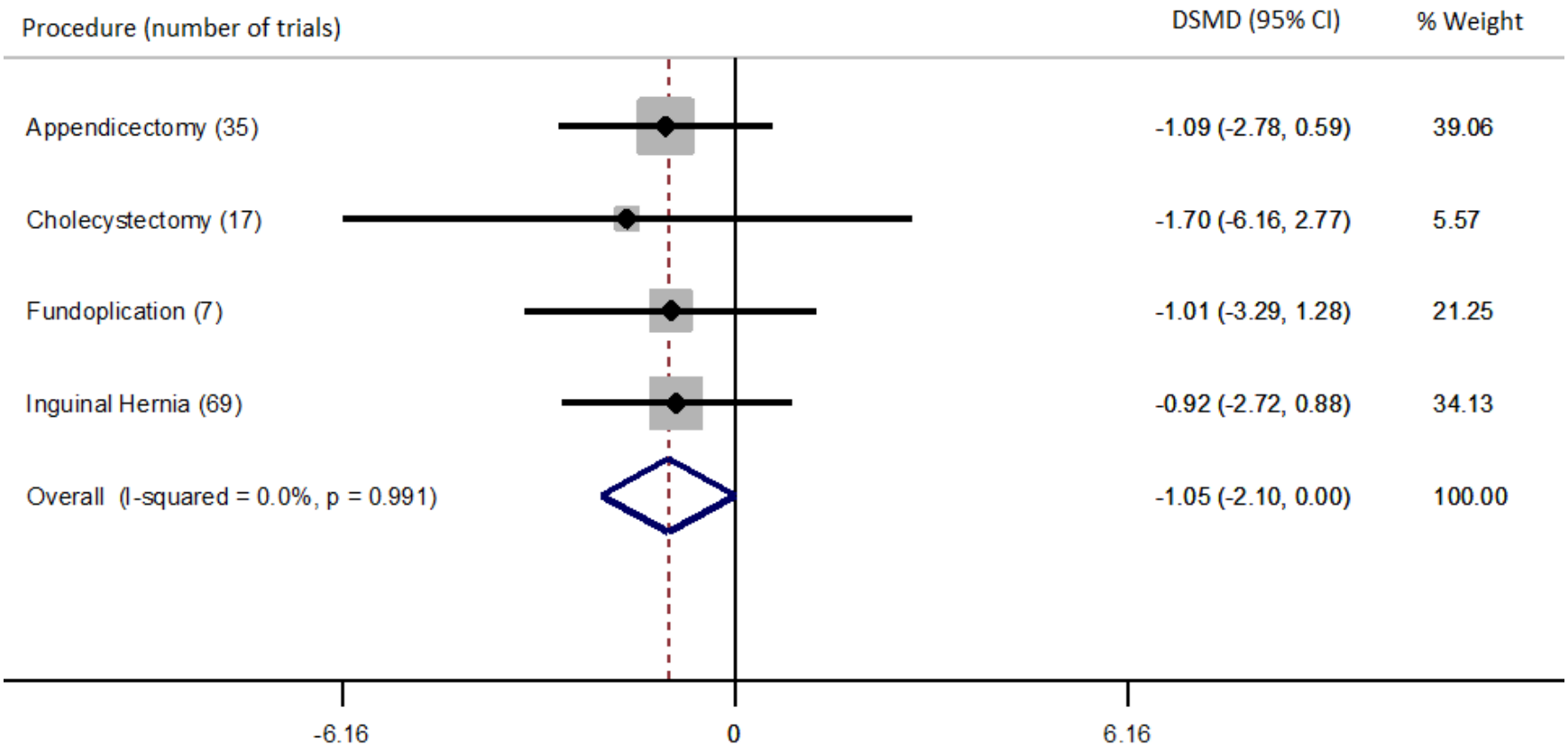


Figure 4.29 Time to recovery forest plot – meta-regression of outcome assessor blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

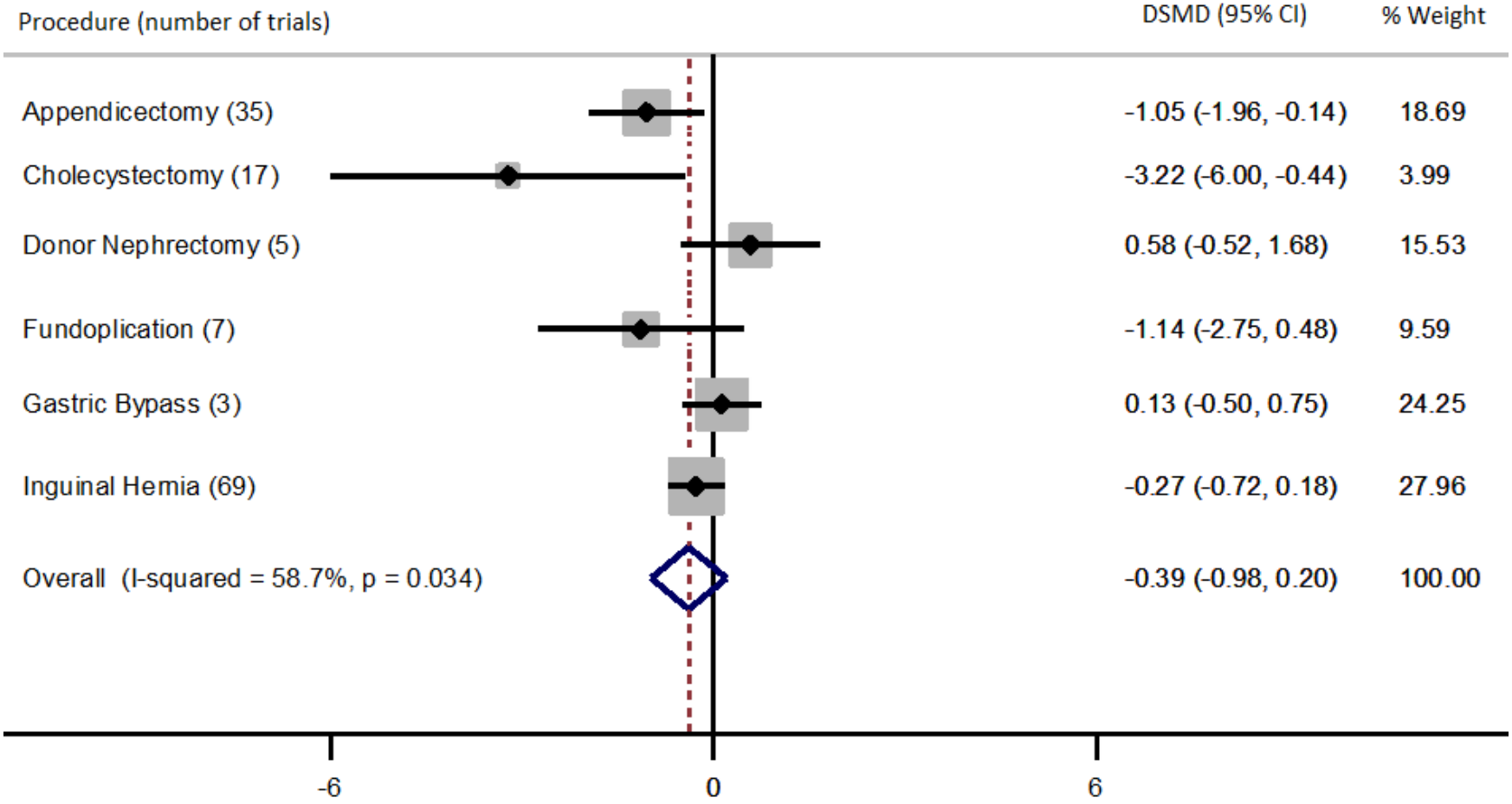


Figure 4.30 Time to recovery forest plot – meta-regression of random sequence generation

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

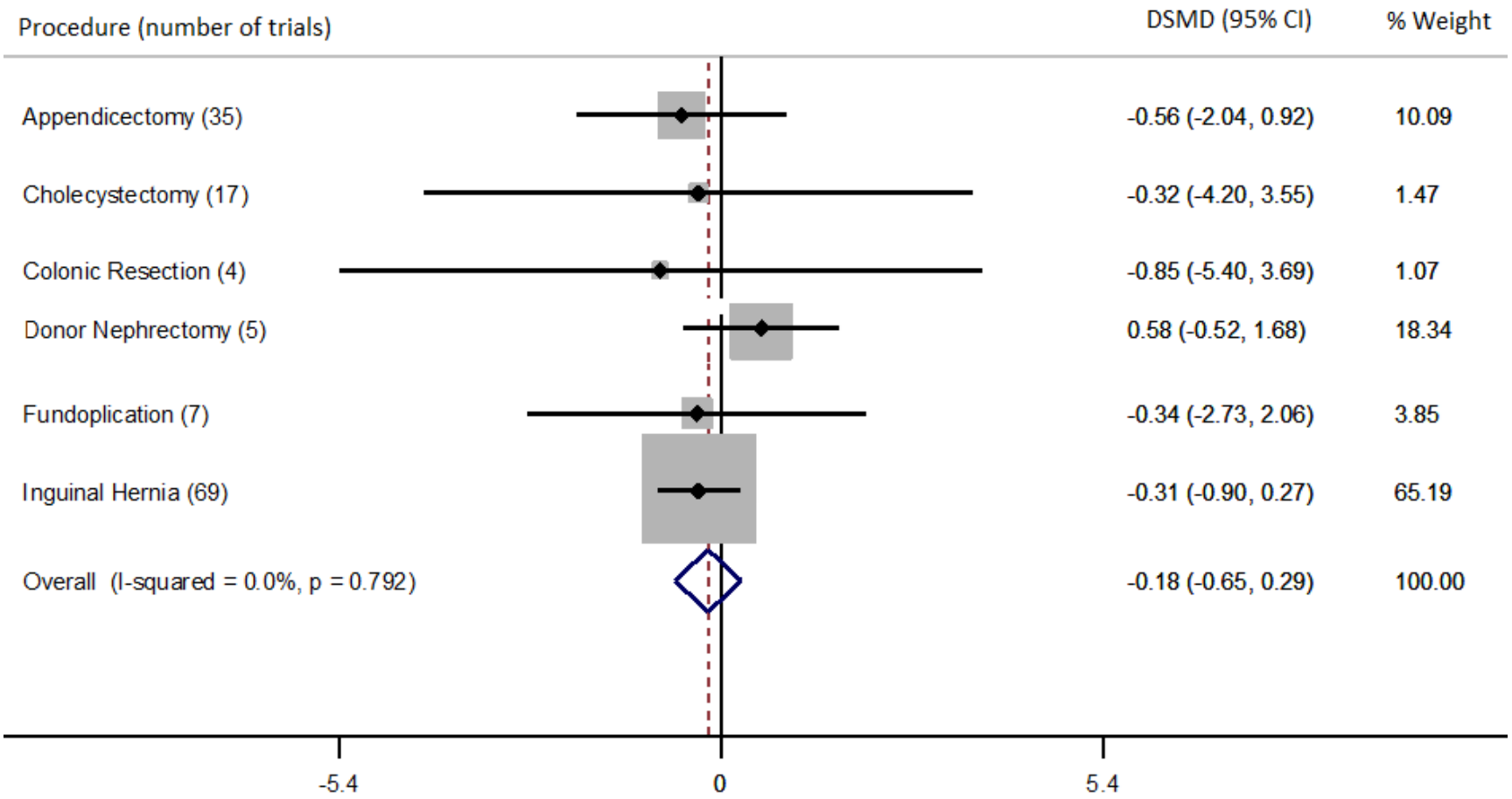


Figure 4.31 Time to recovery forest plot – meta-regression of allocation concealment

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

Short term pain

Pain score data were reported by a total of 122 RCTs for six procedures, with insufficient data available to include fundoplication and gastric bypass trials. Figures 4.32 – 4.37 show the analysis results for each bias-minimisation measure.

RCTs where outcome assessors were blinded reported a significantly smaller difference in short-term pain between laparoscopic and open groups compared to studies where outcome assessors were not blinded (Figure 4.35). This effect was large (1.4 SD), and the I^2 statistic for this analysis showed no evidence of between-study heterogeneity, as did the point estimates for the contributing procedures. Blinding of other groups also influenced the reported results of trials though this was not statistically significant, and with considerable heterogeneity between procedures.

Studies judged to have generated an appropriate randomisation sequence reported a greater difference in short-term pain between laparoscopic and open groups compared to those that were not (Figure 4.36). This result was consistent across procedures, but not statistically significant. Analysis of the effect of allocation concealment showed a similar result though with significant between-procedure heterogeneity and a confidence interval that included zero (Figure 4.37).

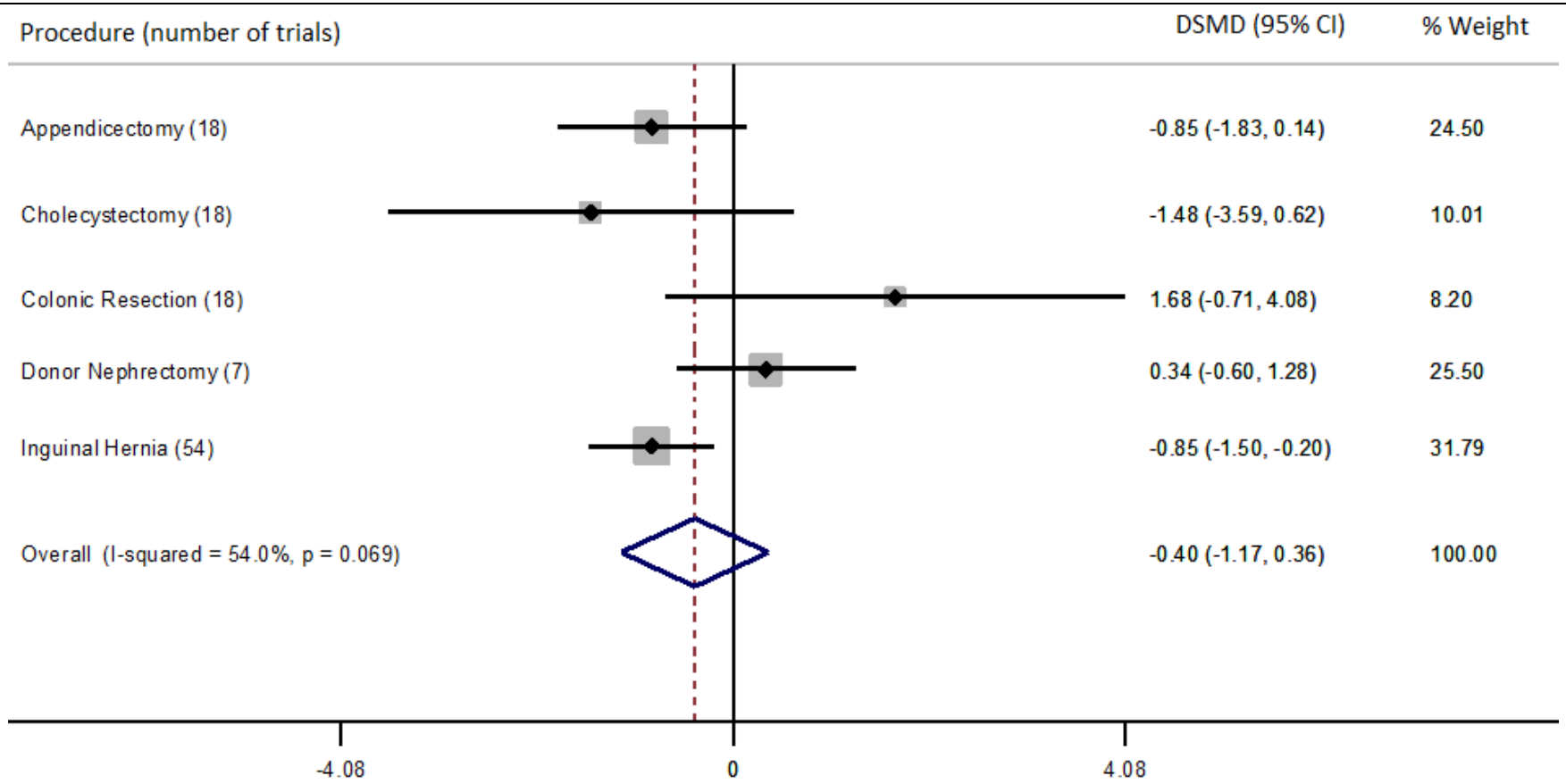


Figure 4.32 Short-term pain forest plot – meta-regression of patient blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

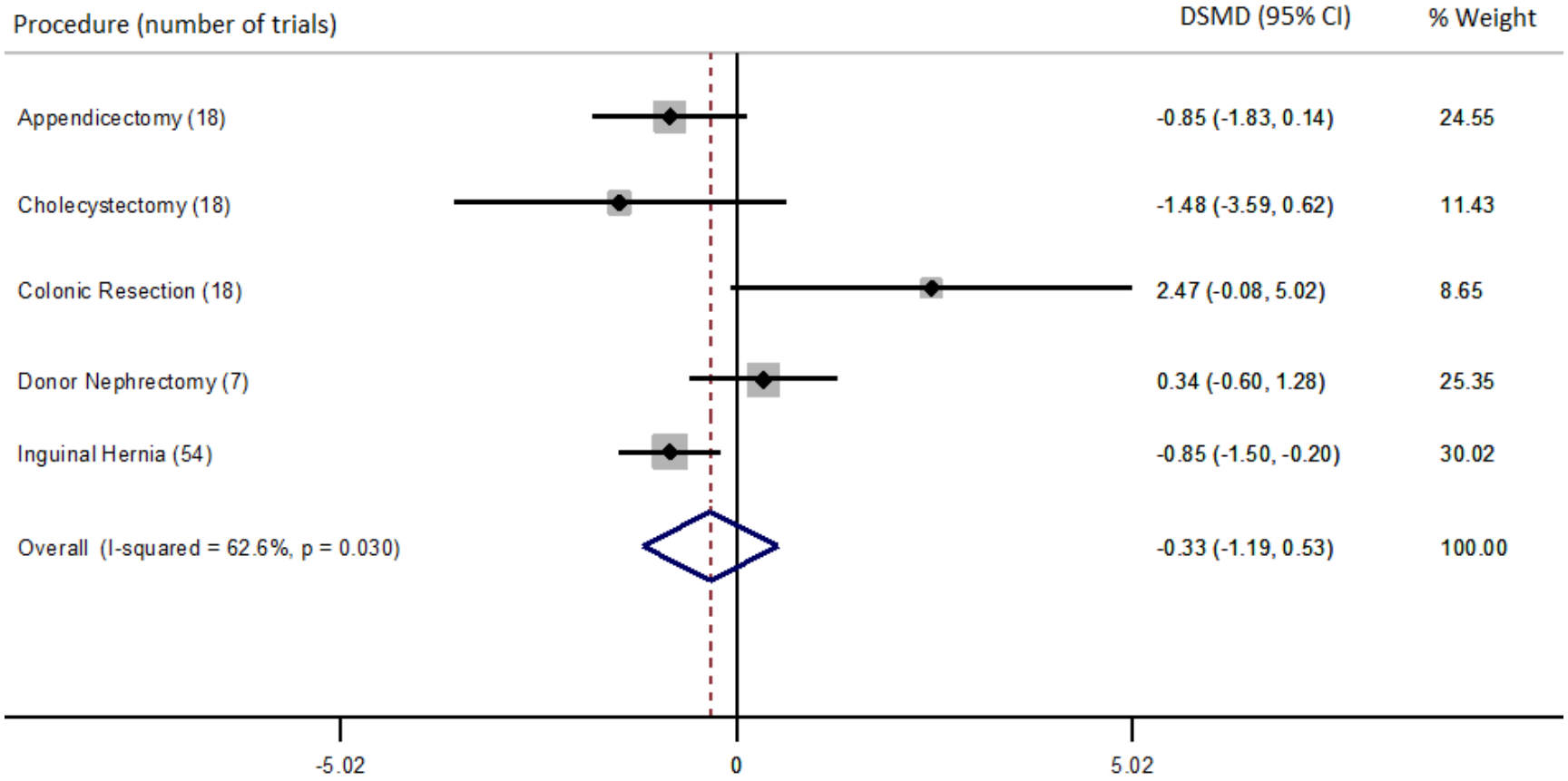


Figure 4.33 Short-term pain forest plot – meta-regression of healthcare staff blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

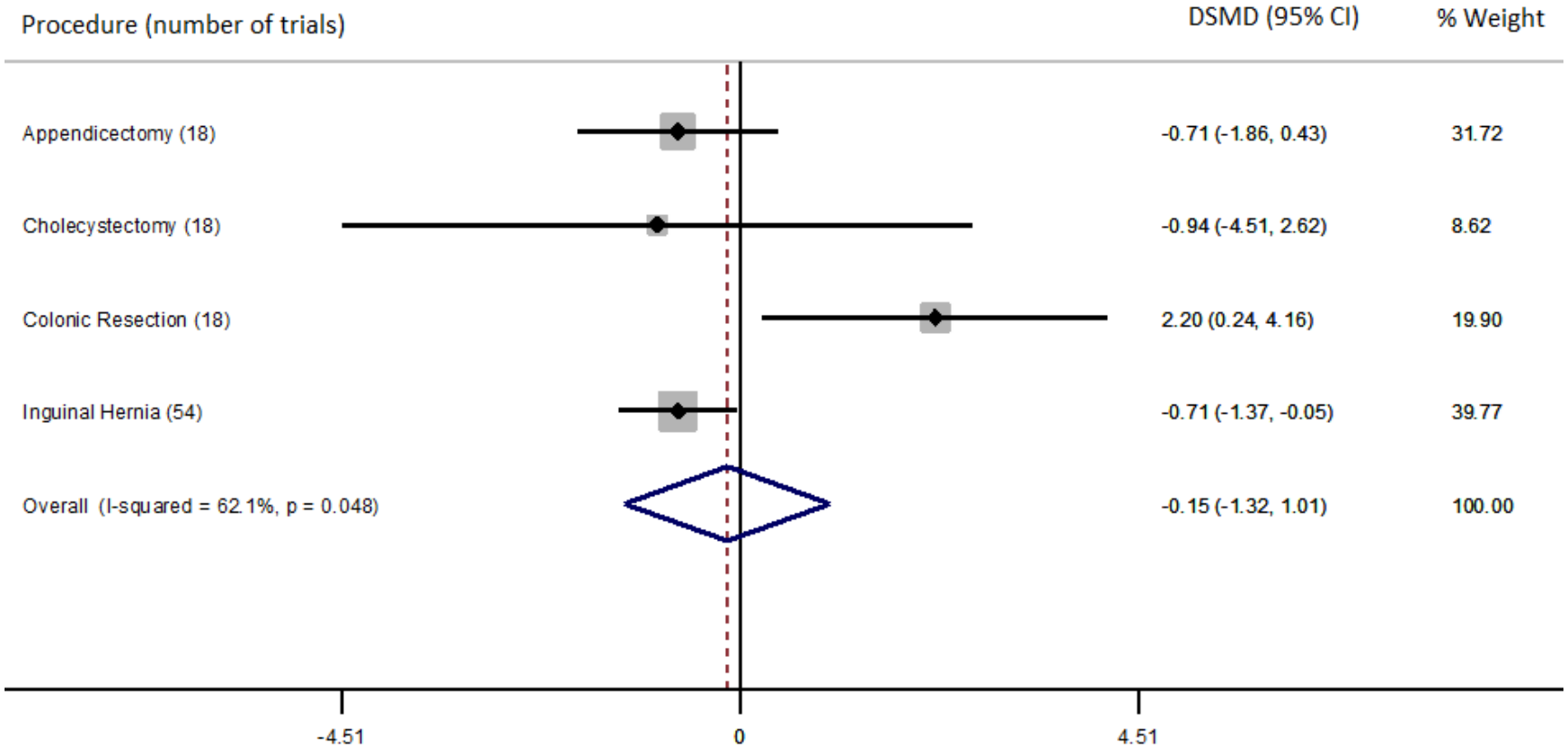


Figure 4.34 Short-term pain forest plot – meta-regression of data collector blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

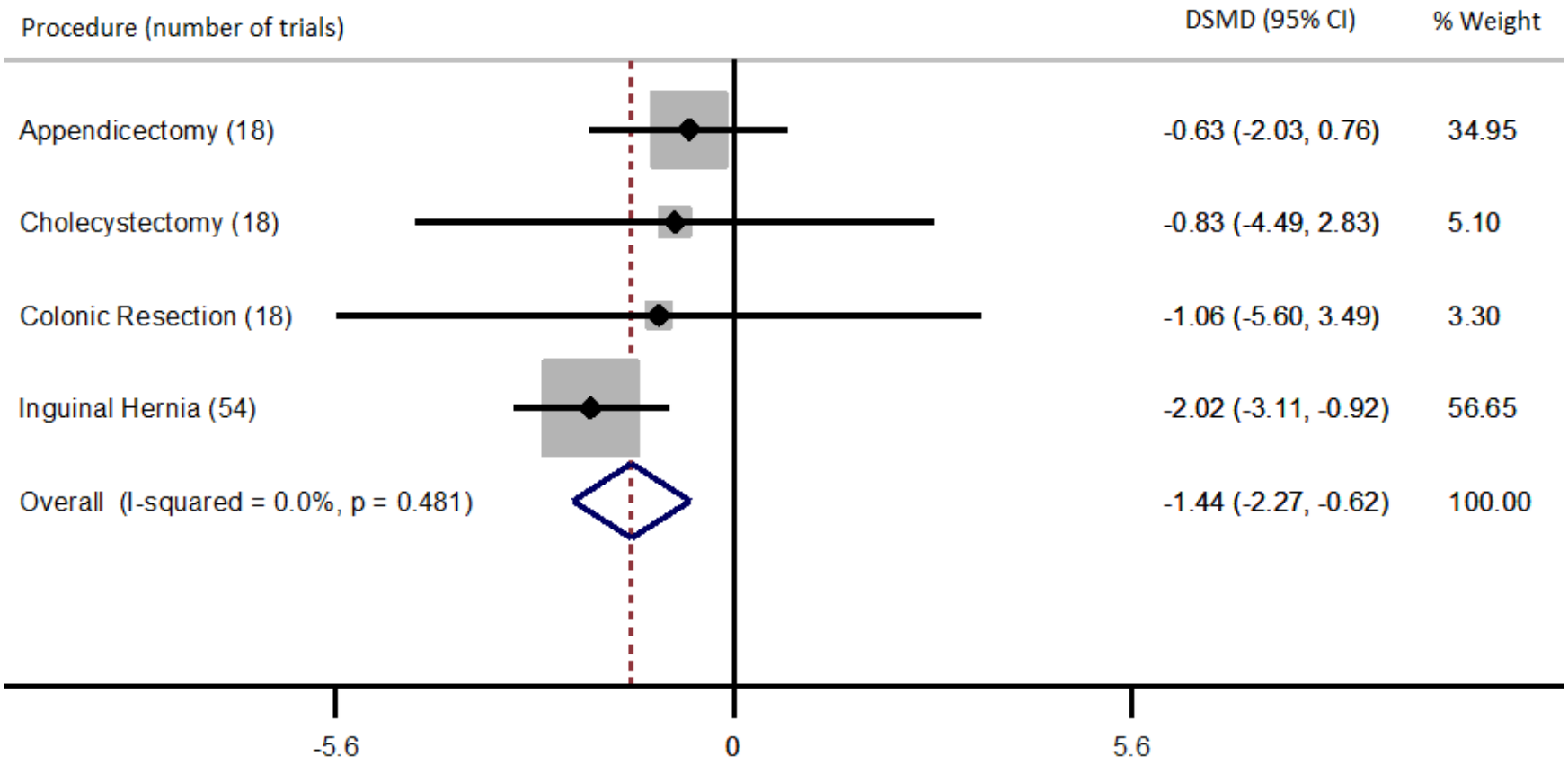


Figure 4.35 Short-term pain forest plot – meta-regression of outcome assessor blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

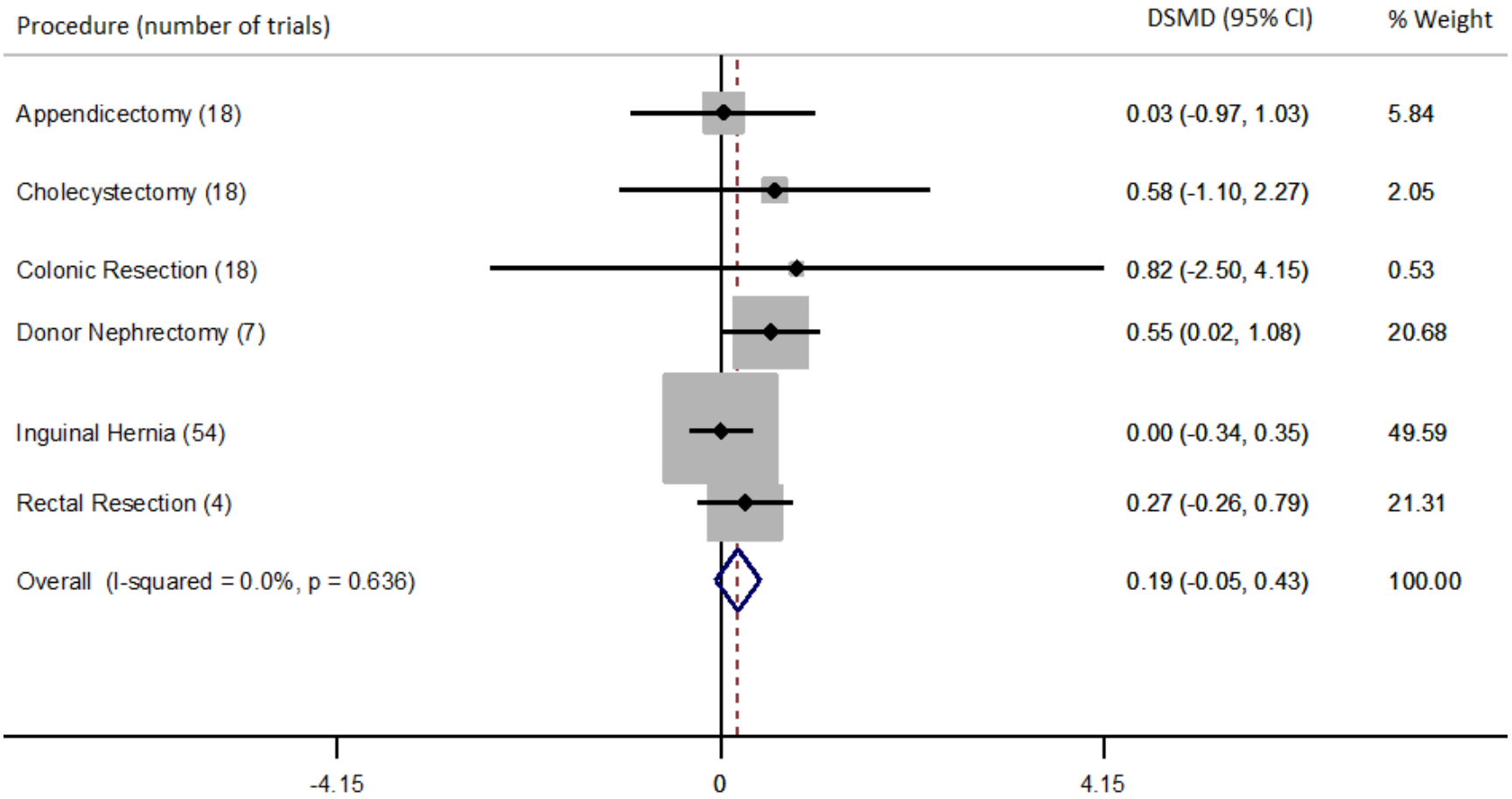


Figure 4.36 Short-term pain forest plot – meta-regression of random sequence generation

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

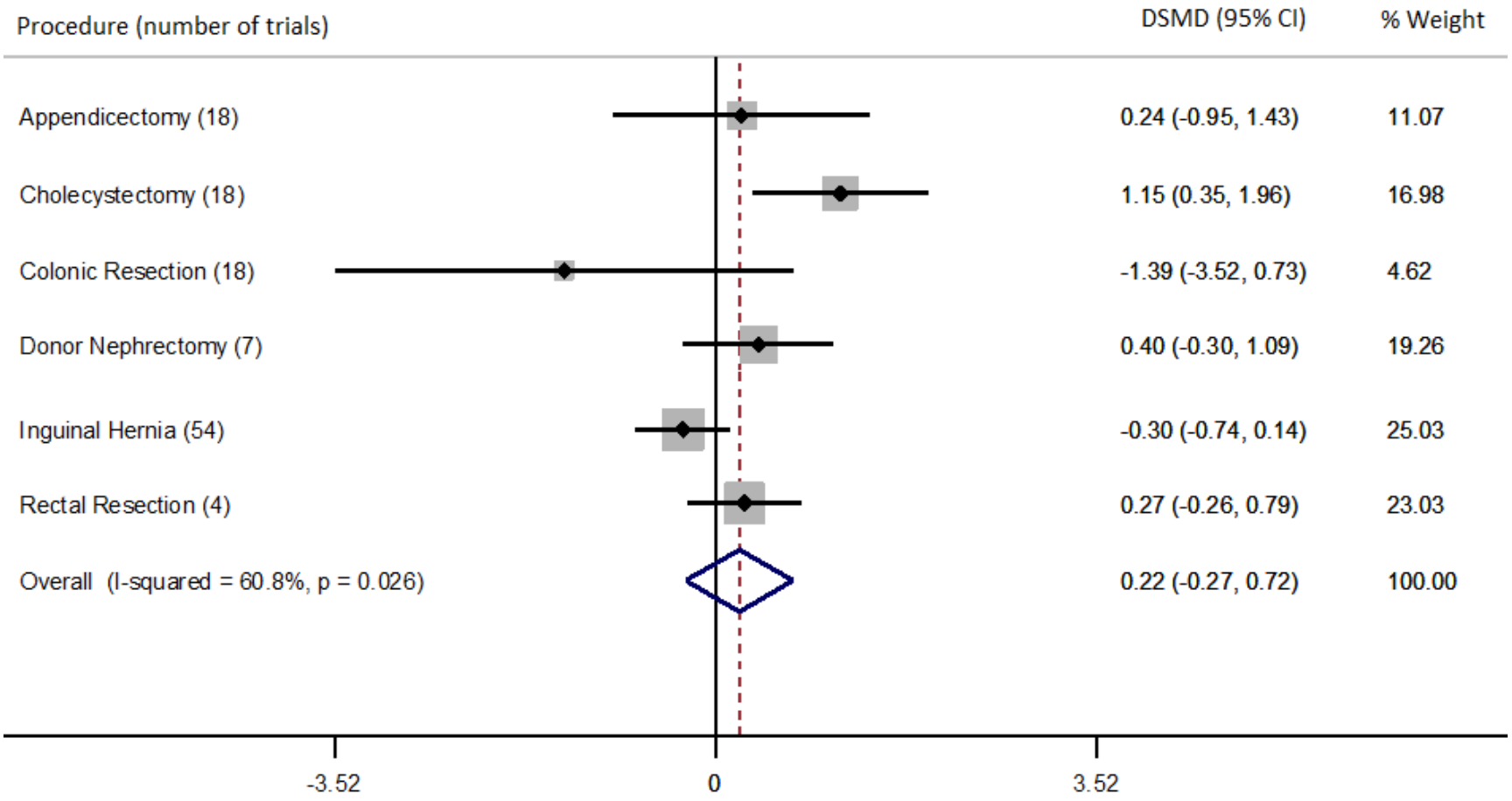


Figure 4.37 Short-term pain forest plot – meta-regression of allocation concealment

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

Long-term pain

Thirty-two trials comparing a laparoscopic and open approach to seven procedures reported this outcome, but a paucity of data meant that only up to three procedures (cholecystectomy, colonic resection and donor nephrectomy) were able to be included in each of the blinding analyses, with data from a total of just twelve trials. Data from RCTs investigating inguinal hernia were also included in the random sequence generation and allocation concealment analyses.

The forest plot summarising the analysis for patient blinding is shown in Figure 4.38, and shows no significant influence on the reported difference in long-term pain. As mentioned earlier however, this should be interpreted with caution as the included data were from a very small number of studies, and there was evidence of substantial between-procedure heterogeneity with an I^2 statistic of over 90%. Analysis results for healthcare staff and data collector blinding were similar (forest plots not shown). Only one procedure (colonic resection) reported sufficient data for outcome assessor blinding analysis with the result suggesting that studies with this form of blinding reported an increased difference in long-term pain (DSMD 1.00, 95% CI 0.57, 1.44). However, this was based on data from just five trials with only one blinded RCT, and between-study heterogeneity was high (I^2 = 100%).

Data for the effect of appropriate random sequence generation and allocation concealment on reported long-term pain results were available from nineteen studies investigating three procedures. Analysis results (Figures 4.39 and 4.40) showed that use of either of these bias-minimisation measures was associated with a greater reported difference in long-term pain between the laparoscopic and open groups. There was no statistical evidence of heterogeneity (I^2 = 0%), though the point estimates for each procedure varied in both analyses. These results were not statistically significant.

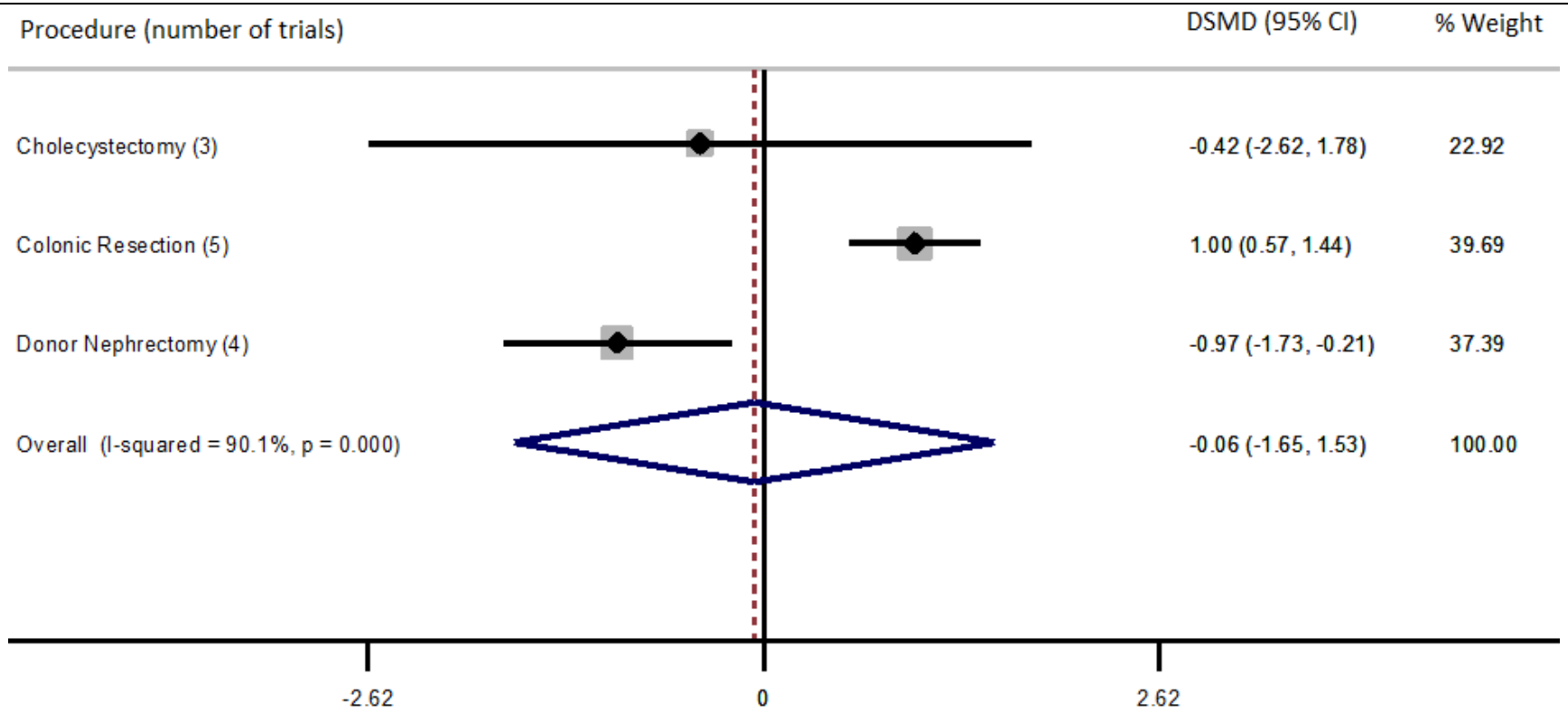


Figure 4.38 Long-term pain forest plot – meta-regression of patient blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

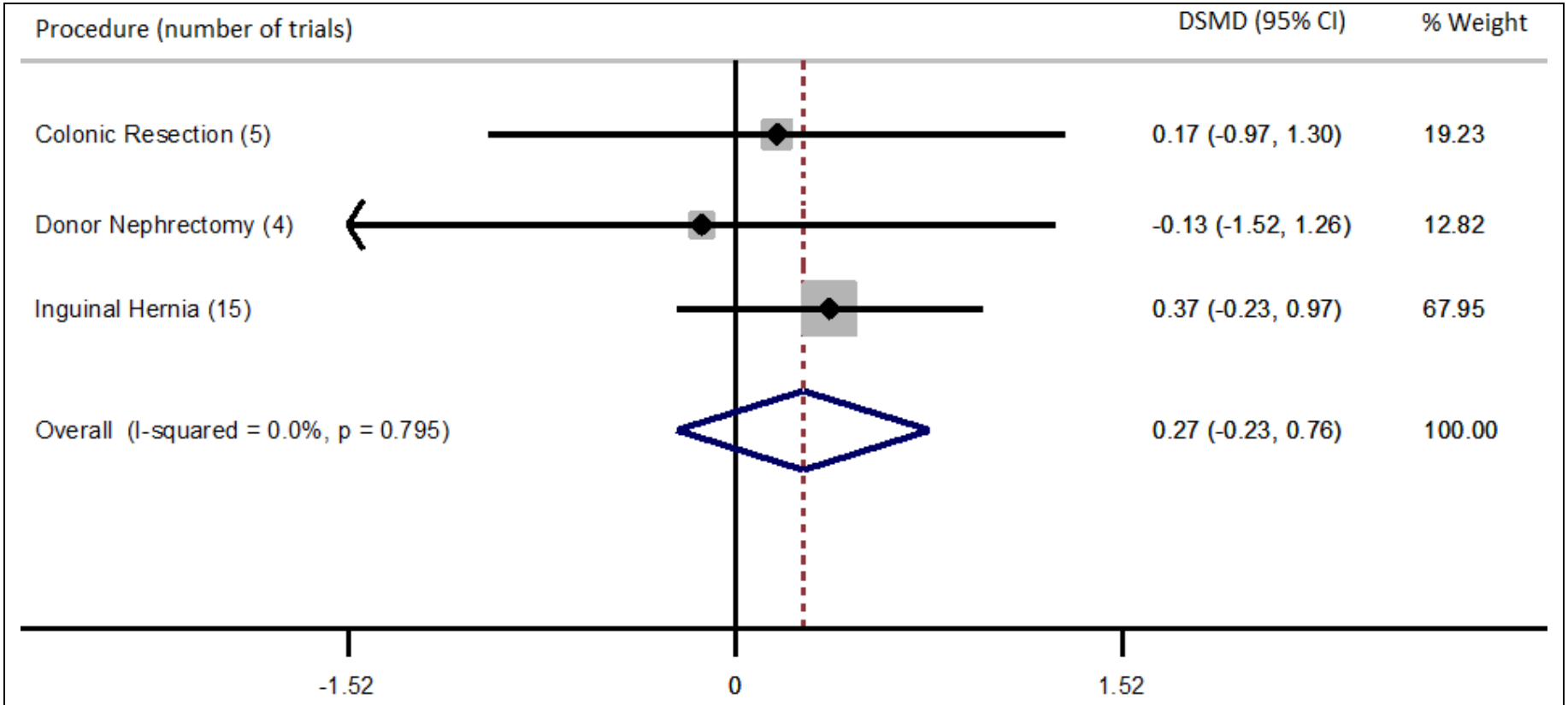


Figure 4.39 Long-term pain forest plot – meta-regression of random sequence generation

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

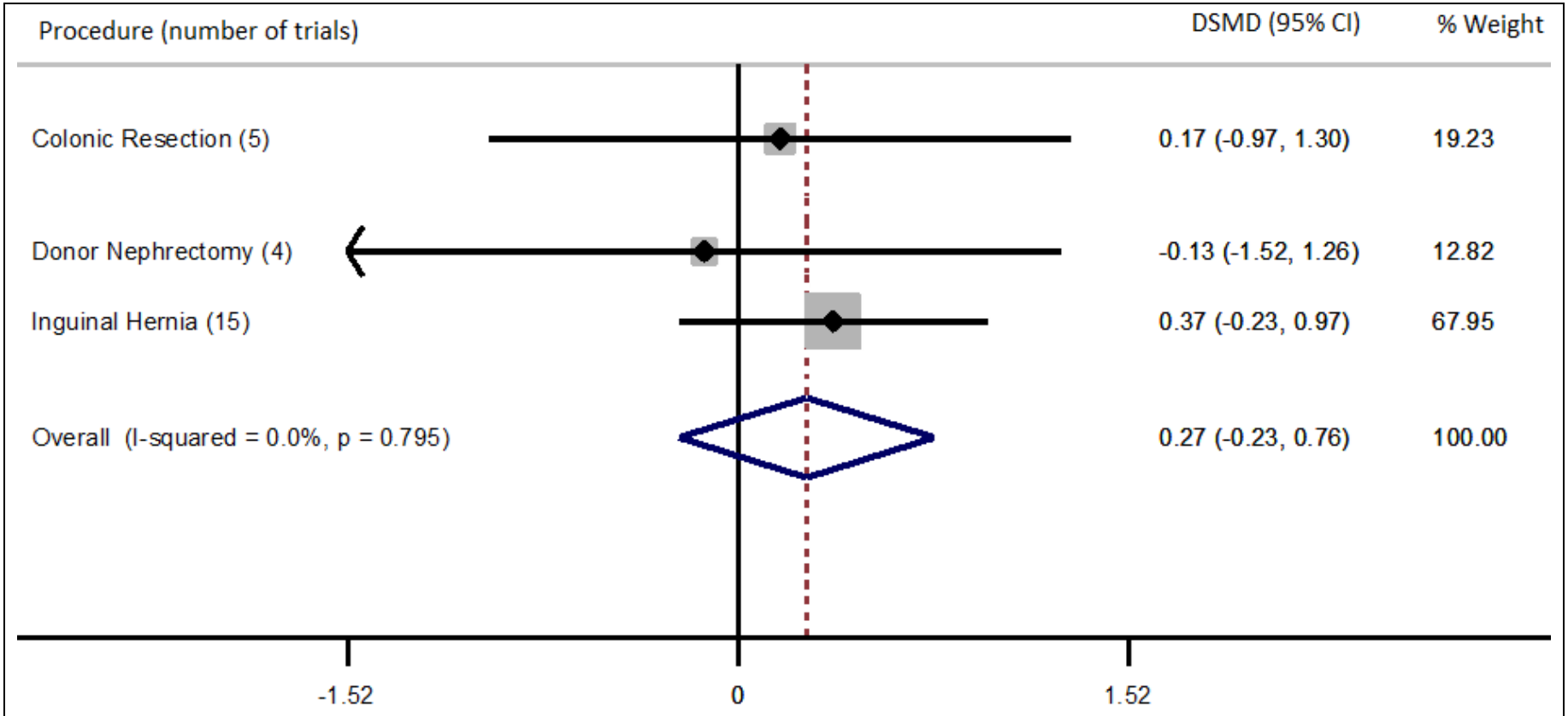


Figure 4.40 Long-term pain forest plot – meta-regression of allocation concealment

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

Return of intestinal function

This outcome was not commonly reported, with time to first passage of flatus reported by 32 RCTs investigating four procedures (appendicectomy, cholecystectomy, colonic resection and rectal resection), and time to first passage of bowel motion reported by 33 RCTs for five procedures (the same four procedures above with the addition of rectopexy). However, as few of these trials used bias-minimisation, the number of procedures included in each analysis for this outcome were much fewer.

Data for only one to two procedures (colonic and rectal resection) were able to be included in the meta-regressions investigating the effect of each blinding measure on reported time to first passage of flatus and time to first bowel motion. All these analyses showed a smaller reported difference in time to return of intestinal function between studies that used each blinding measure and those that did not (Figure 4.41 shows one example), though confidence intervals were wide (all included zero), and some of the analyses showed evidence of significant heterogeneity.

RCTs assessed as appropriately generating a randomisation sequence and concealing it effectively reported a smaller difference in time to return of intestinal function between laparoscopic and open groups compared to other studies (Figures 4.42 – 4.45), though this difference was often not statistically significant. There was no statistical evidence of significant heterogeneity for these analyses.

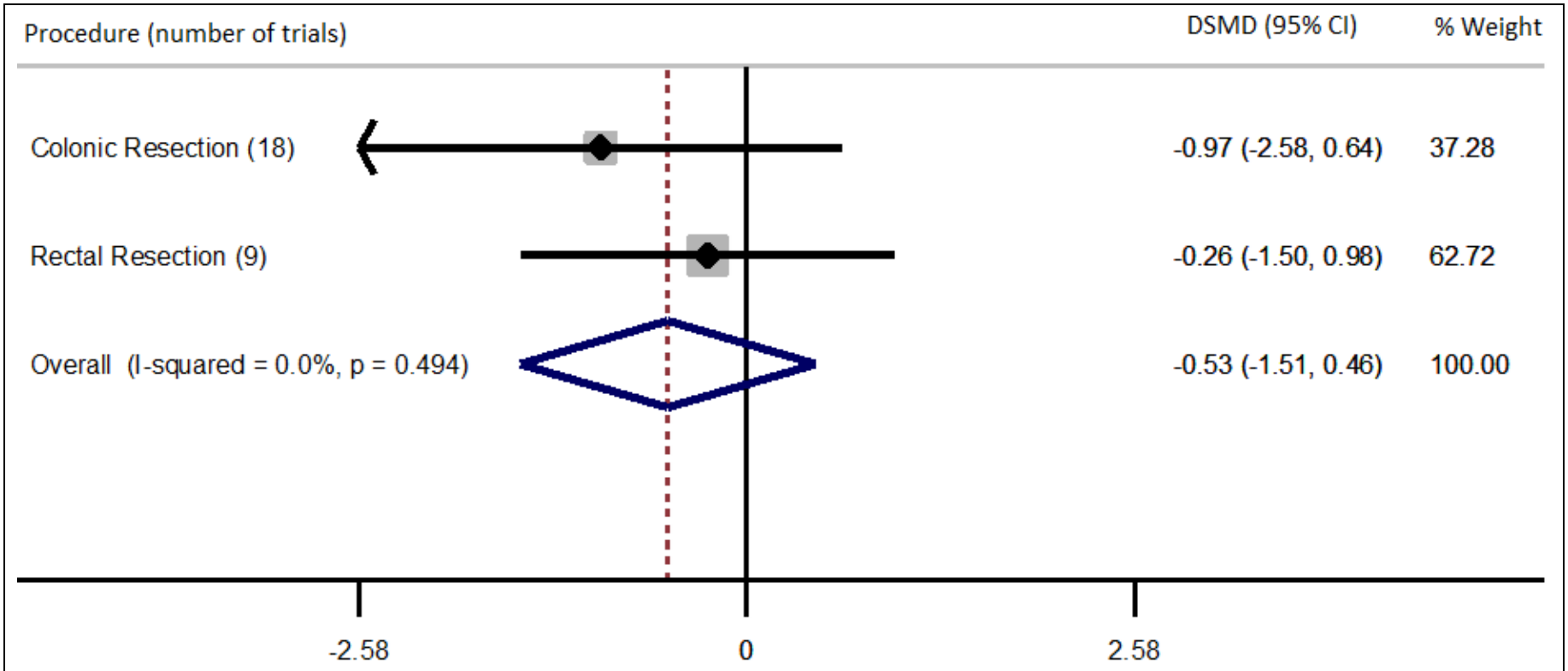


Figure 4.41 Return of intestinal function (time to first passage of flatus) forest plot – meta-regression of outcome assessor blinding

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

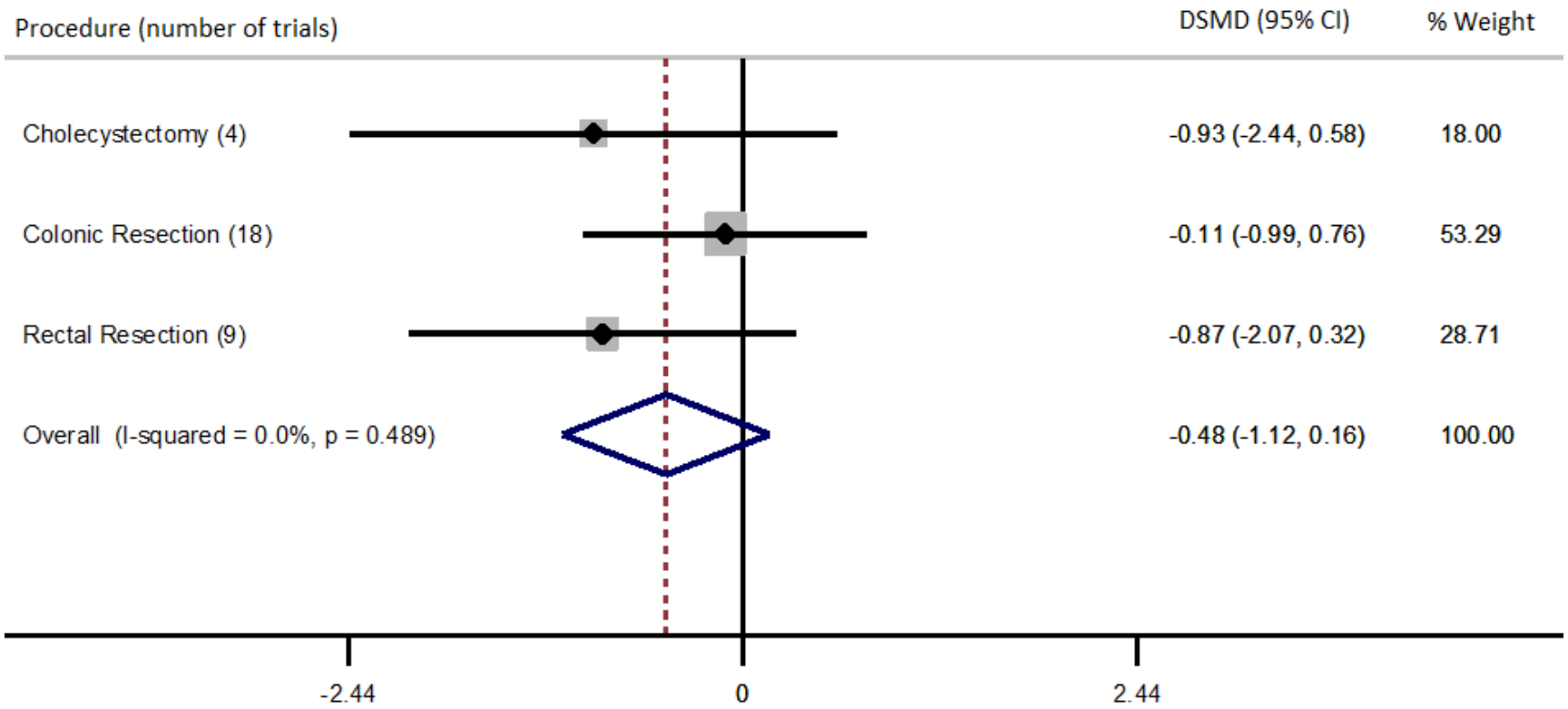


Figure 4.42 Return of intestinal function (time to first passage of flatus) forest plot – meta-regression of random sequence generation

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

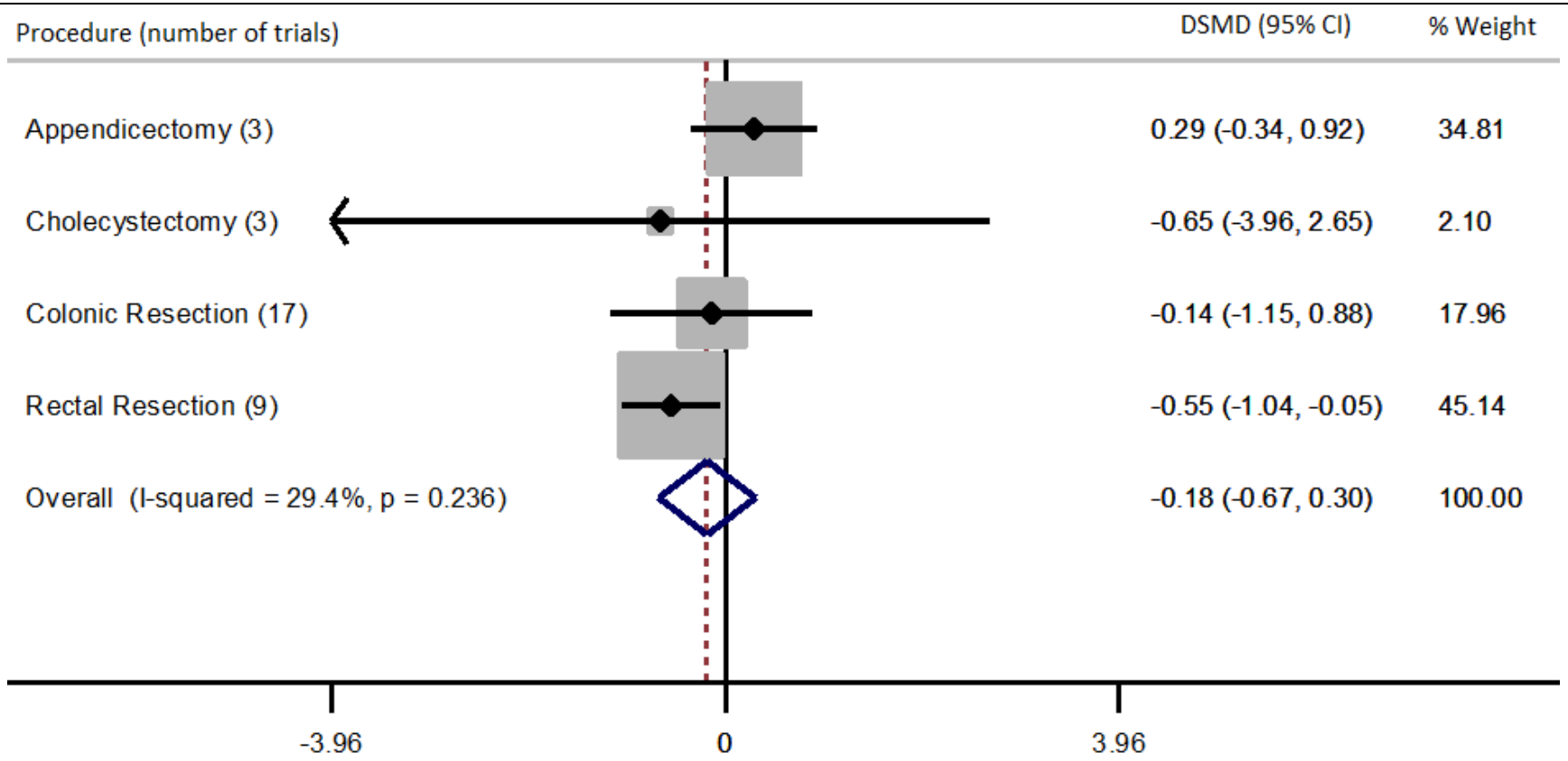


Figure 4.43 Return of intestinal function (time to first passage of bowel motion) forest plot – meta-regression of random sequence generation

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

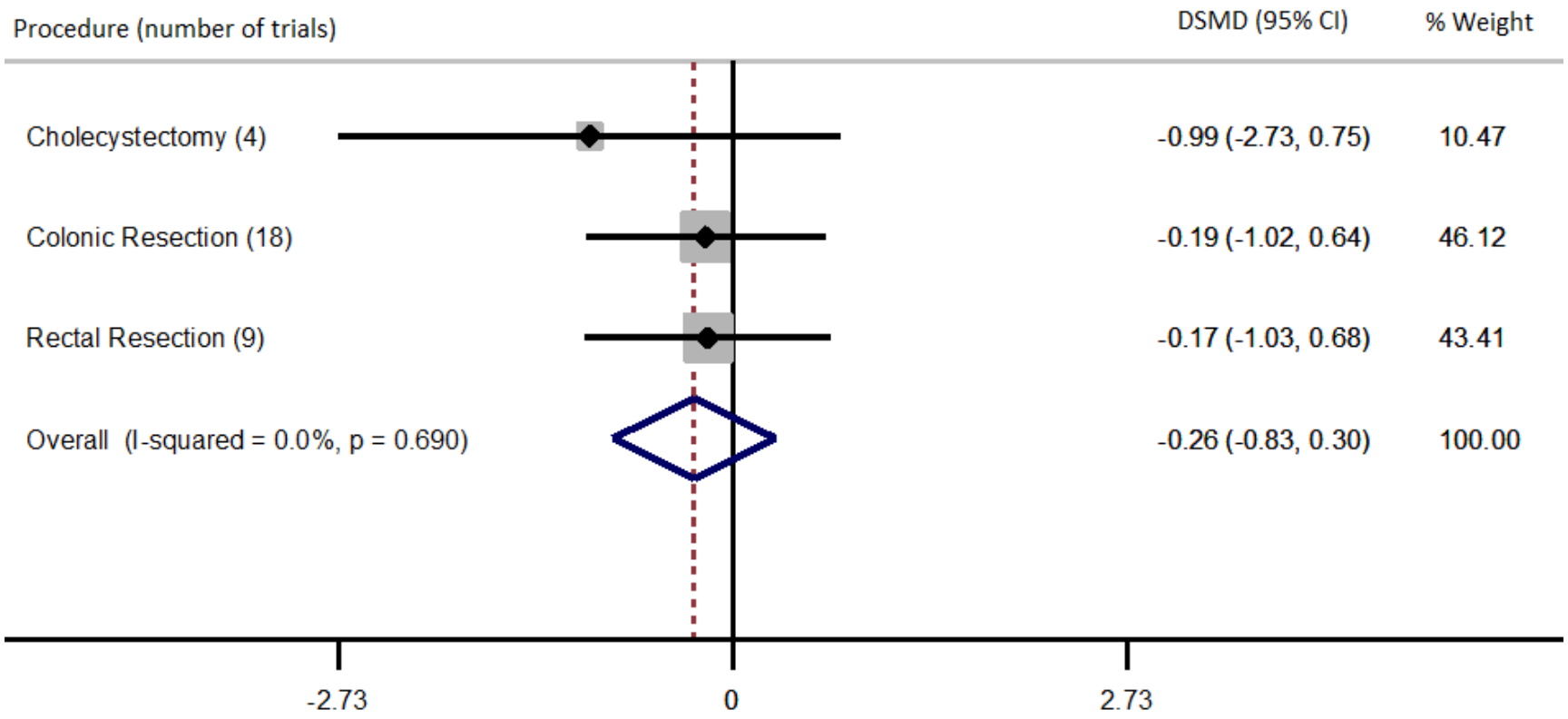


Figure 4.44 Return of intestinal function (time to first passage of flatus) forest plot – meta-regression of allocation concealment

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

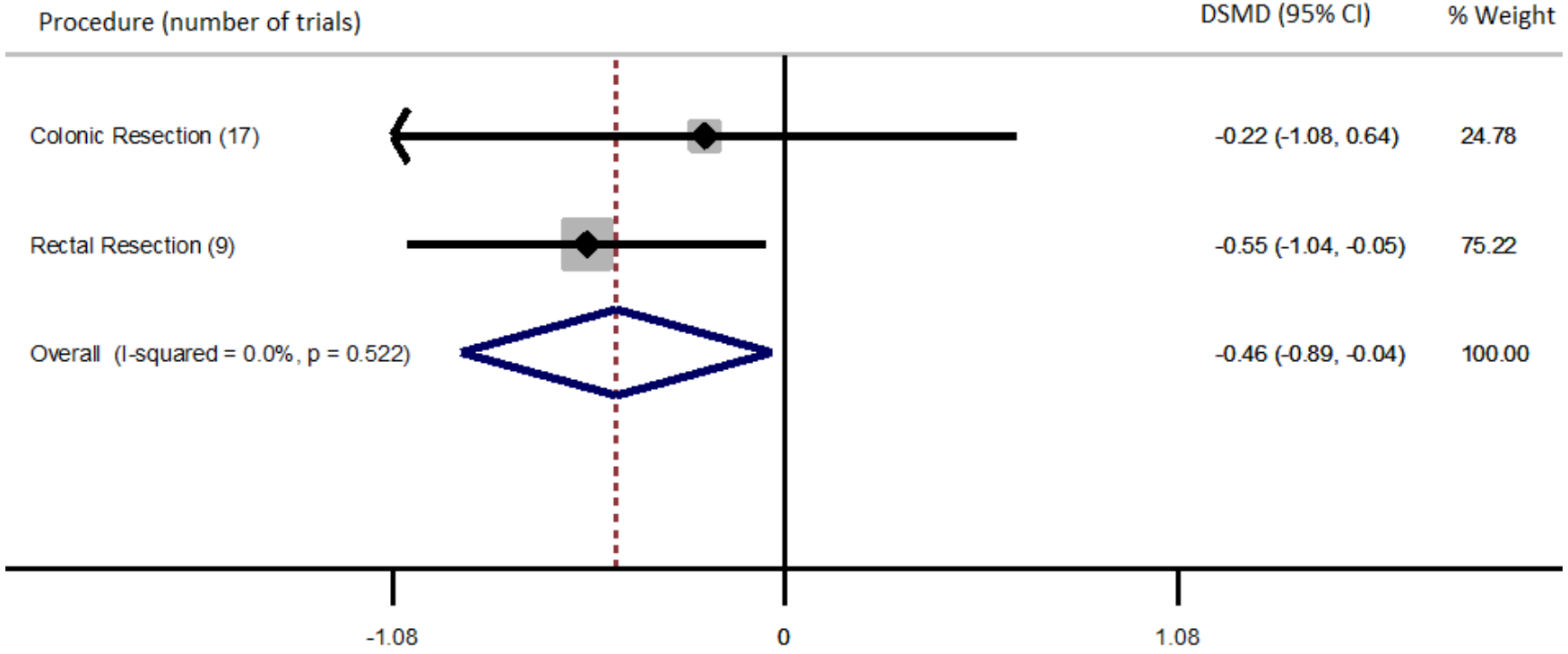


Figure 4.45 Return of intestinal function (time to first passage of bowel motion) forest plot – meta-regression of allocation concealment

Unit is standard deviations. Weights are based on random effects meta-analysis. Values to the left of midline indicate that studies that used this bias-minimisation measure reported a small difference compared to studies that did not.

95% CI = 95% confidence interval. DSMD = Difference of standardised mean differences.

4.5 Discussion

This study shows that trials comparing a laparoscopic and open approach to general surgical procedures reported significantly smaller differences in outcome measures between the intervention groups when patients, healthcare staff or outcome assessors were blinded, and when random sequence generation was performed correctly. This finding is consistent across procedures and multiple outcome measures, including outcomes where the endpoint is reached after un-blinding such as time to recovery. Blinding of data collectors and concealment of the allocation sequence were also found to be influential but to a lesser extent, with no statistically significant differences in the reported results of RCTs that used either of those two measures compared to those that did not.

Quantitative interpretation of the results using rules of thumb for SMDs (Higgins and Green, 2011) alone may suggest that the influence of lack of these bias-minimisation measures is small (SD < 0.4). However, RCTs comparing a laparoscopic and open approach have commonly reported similar small differences between the intervention groups (McCulloch et al., 2002), but these have been interpreted as clinically important and have contributed to change in the accepted standard surgical practice (Russell, 1995). Systematic bias arising from failure to use bias-minimisation measures may have therefore contributed to a type I error in some of those trials.

Several meta-epidemiology studies have concluded that RCTs where blinding is not performed report an exaggerated treatment effect (Savovic et al., 2012; Schulz et al., 1995; Wood et al., 2008). Similar results have been reported from studies investigating the influence of random sequence generation (Siersma et al., 2007). These studies have however been criticised for being too heterogeneous (Hrobjartsson et al., 2012) as they pooled meta-analyses from a wide range of disciplines reporting on a variety of different outcome measures, and some relied on a binary (yes or no) definition of blinding without differentiating between the various forms blinding can take (Devereaux et al., 2001). Furthermore, these studies relied on the risk of bias assessments of the included meta-analyses, which may have used different definitions or relied on ambiguous statements such as “this study was double-blinded” (Hill et al., 2002; Schulz and Grimes, 2002). The validity of these results, particularly in relation to procedural trials which were under-represented in the data pool, is therefore questionable. Other studies have attempted to minimise heterogeneity by analysing data from studies that reported both blinded and un-blinded outcome

assessment thus ensuring that the same outcomes were being compared (Hrobjartsson et al., 2012, 2013; Hrobjartsson et al., 2014). Only a small number of RCTs are designed in this manner however, so such studies have included very limited data. Additionally, these studies could only assess the influence of one form of blinding.

The present study incorporated design elements from both types of studies including individual trial data, a standardised comprehensive risk of bias assessment across all included studies, a defined set of relevant outcome measures and meta-epidemiological analysis, as well as other elements such as an assessment of individual forms of blinding and standardisation of the intervention comparison (laparoscopic versus open). The outcome measures used in this study are more likely to be influenced by systematic bias arising from trial design and are patient-relevant endpoints commonly reported in studies comparing surgical techniques. All of these features allowed for a novel, systematic and pragmatic assessment of the influence of each of several bias-minimisation strategies on the reported results of surgical RCTs in a manner that substantially minimises heterogeneity and ensures external validity.

There are some potential limitations to this study. The proportion of blinded studies was relatively small for some procedures, which may affect power, and there were insufficient data to allow for an assessment of the influence of data analyst blinding. Although this may be due to incomplete reporting of methods leading to a high proportion of unclear risk of bias assessments, the procedure and trial selection process was systematic and sensitive, so this is more likely reflective of the relative paucity of blinded trials in the surgical trial literature (Karanicolas et al., 2008), which highlights the need for the present study.

The statistical analysis was performed as a univariate meta-regression model, meaning that the result for each bias-minimisation measure did not independently take into account the presence or absence of other measures. This means that confounding may be contributing to some of the findings. Multivariate meta-regression was not possible due to the low proportion and number of blinded trials for each procedure, and combining trials across procedures to facilitate this would have introduced significant heterogeneity and decreased the validity of the findings. The consistency of the findings across outcomes and procedures for specific bias-minimisation measures would suggest that substantial confounding is unlikely.

Only one risk of bias assessment was completed for each included study, instead of a breakdown by outcome, which may affect the validity of the results with regards to end-points that are reached well beyond discharge from hospital (and un-blinding) such as time to recovery. However, the main purpose of this study was to pragmatically assess the influence of blinding *per se* within an RCT's design on outcomes which are commonly reported in surgical RCTs, and it is acknowledged that it is difficult to maintain blinding in surgical trials beyond discharge, particularly of patients and healthcare staff. It is also pertinent to note that even such long-term outcomes were significantly affected by the presence or lack of the studied measures, suggesting that their bias-minimising effect extends well beyond their period of implementation in a study.

The Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz et al., 2010), a comprehensive set of guidelines on the reporting of randomised trials produced by an international expert group, specifies measures such as blinding and random sequence generation as features of robust RCT design. Some authors have argued that blinding is too difficult or unrealistic in surgical RCTs, and that non-blinding may not materially alter results (Patel et al., 2013; Pham et al., 2009; Vinuela et al., 2012). This systematic meta-epidemiological study, which included trial data from over 300 individual surgical RCTs, shows that lack of patient, healthcare staff and outcome assessor blinding, and lack of adequate random sequence generation, systematically alter the results of trials comparing different surgical approaches, which may lead to erroneous results and conclusions. These findings need to be taken into account when interpreting the results of published studies, and should be used to guide the design of future surgical trials. Further efforts are required to facilitate and disseminate the implementation of effective blinding in procedural trials.

4.6 Conclusion

The present study used meta-epidemiological methods at an individual trial level to comprehensively assess the effect of bias-minimisation measures including blinding on the reported outcomes of surgical RCTs comparing a laparoscopic and open approach to common abdominal surgical procedures. Although several previous studies have investigated the influence

of such measures on RCT results in general, none had specifically examined this effect on procedural trials where additional challenges to effective blinding exist.

The results of this study show that RCTs that did not use blinding or adequate random sequence generation reported a significantly greater difference between treatment groups compared to trials where these bias-minimisation measures were used. This may lead to exaggerated differences in outcome measures in individual trials, and could also influence the results of subsequent meta-analyses. Blinding should be implemented in procedural RCTs wherever feasible to avoid systematic bias.

CHAPTER FIVE

Conclusions

5.1 Summary

The continuous development and refinement of techniques and treatments has long been a key attribute of the discipline of surgery (Brennan, 2008), in a quest to offer patients optimal care (Potter et al., 2014). Robust evidence derived from RCTs and subsequent MAs is therefore an indispensable tool in modern surgical practice. There are several challenges however to the development of this evidence. This thesis has addressed two of these challenges, namely the statistical synthesis of RCT data where multiple treatment comparisons exist, and the influence of non-blinding and other potential sources of bias on the results of surgical RCTs.

The application of NMA methodology to surgical research synthesis to enable inclusive analysis of all available data and succinct conclusions was demonstrated in this thesis, using two examples. Both were conducted in accordance with the Cochrane Collaboration's recommended methodology (Higgins and Green, 2011) and PRISMA guidelines (Hutton et al., 2015; Moher et al., 2009; Shamseer et al., 2015) to ensure rigor and validity.

International guidelines groups have regarded preoperative carbohydrate loading as an integral part of enhanced recovery protocols and advocated for its routine use for all elective surgery (Cerantola et al., 2013; Gustafsson et al., 2013; Lassen et al., 2012; Mortensen et al., 2014; Nygren et al., 2013), even though individual RCTs had shown quite variable results. The NMA detailed in Chapter Two is the first study to include all data from all trials, regardless of the control treatment used in contributing RCTs. It showed conclusively that there was no additional benefit gained from CHO loading compared to water across all the clinically relevant outcomes assessed. This finding has already led to a change in the guidelines of two major international surgical societies (The American Society of Colon and Rectum Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons) (Carmichael et al., 2017), and reflects an evidence-based change in practice. The paper reporting this NMA has been cited more than 25 times since its recent publication (Amer et al., 2017).

Chapter Three of this thesis describes an NMA of surgical treatments for GORD, a very common condition for which multiple different surgical procedures exist. International surgical society recommendations were that the choice of procedure should be left to the individual surgeon due to conflicting data (Stefanidis et al., 2010), despite more than 50 RCTs involving thousands of patients published over more than four decades. The NMA detailed in Chapter Three included all published trials, analysed all of the available data and produced an objective ranking of the different procedures according to clinically important outcomes of benefit and harm. It showed that the best balance of risk and benefit for patients undergoing surgical treatment of GORD is obtained with posterior partial fundoplication. This NMA represents the first comprehensive synthesis of all the available RCT data and provides a definite answer to a clinical question that had been the subject of debate among surgeons for years (Amer et al., 2018).

It has been known for some time that failure to implement bias-minimisation measures in clinical trials systematically alters the results and may lead to incorrect conclusions (Savovic et al., 2012; Schulz et al., 1995; Wood et al., 2008). Before now this issue had not been examined specifically in procedural trials despite the fact that procedures have a greater placebo effect than other forms of treatment (Kaptchuk et al., 2000; McRae et al., 2004) and may therefore be more prone to systematic bias. In addition, some of the standard bias-minimisation measures such as blinding are more difficult to implement in surgical trials. Chapter Four reports on a comprehensive meta-epidemiological study using trial data from 316 individual RCTs to explore this question in detail, using the practical example of trials that compared laparoscopic versus open access for common abdominal surgical procedures. The results showed that trials where blinding or adequate random sequence generation were not performed reported a greater difference between the laparoscopic and open groups for endpoints such as length of stay and postoperative complication rates, compared to RCTs that used those bias-minimisation measures. These findings help to better inform the interpretation of already published trials, and guide the design of future surgical trials to ensure their objectiveness and validity.

5.2 Future directions

NMA methodology can be used to answer many more surgical research questions. During the course of this PhD, the author has been involved in three other collaborations using NMA methodology to assess the treatment options for early hepatocellular carcinoma (Swan et al.,

2017), the surgical management of obesity (Grainger et al., 2018) and bowel preparation prior to colorectal surgery (Woodfield et al., 2017). Many more clinically relevant questions can be answered using NMA methodology where sufficient data exist to enable this. This potential has been a recurring theme in discussions following presentation of components of this thesis at national and international surgical meetings (List of Awards, Grants and Presentations).

While it is important to produce trial reviews that can inform evidence-based recommendations, it is equally important that there is timely uptake of this information into clinical practice. Although many surgeons were among the early pioneers of RCTs, some recent qualitative studies have raised concerns regarding surgeons' attitudes and uptake of RCT and systematic review findings (Lassen et al., 2005; Melis et al., 2010; Potter et al., 2014; Slim et al., 2004). This is in contrast to other surveys that concluded that modern surgical practice is evidence-based (Howes et al., 1997; Kenny et al., 1997; Kingston et al., 2001). All of these studies were conducted in Europe and North America, and there is little information about attitudes among the surgical community in Australasia. Michael Solomon and colleagues (Gattellari et al., 2001) conducted an Australasian survey and found mixed results: while most respondents were positive towards RCTs, they were sceptical regarding the applicability of the results to their everyday practice. However, this study was restricted to colorectal surgeons and is more than 15 years old. More information on current attitudes towards evidence-based practice is required through a large representative survey of Australasian surgeons across a range of surgical disciplines. This will help determine whether additional interventions and programmes are required to ensure recognition and timely uptake of high quality evidence.

Finally, the importance of considering blinding and other bias-minimisation measures in evaluating current evidence and future surgical RCT design needs to be prioritised. Initiatives such as the Balliol Colloquia a decade ago may go some way in achieving this by bringing together experts and facilitating discussion, consensus and recommendations (Lancet, 2009; McCulloch et al., 2009). The inclusion of material on bias and trial design in courses for trainees and surgeons, such as the CLEAR (Critical Literature Evaluation and Research) course run by the Royal Australasian College of Surgeons (RACS, 2019) and similar courses in other jurisdictions (Potter et al., 2014) (Martin et al., 2003), will help increase awareness in the surgical community of these issues.

REFERENCES

Abraham, N.S. (2006). Will the dilemma of evidence-based surgery ever be resolved? ANZ J Surg *76*, 855-860.

Amer, M.A., Smith, M.D., Herbison, G.P., and McCall, J.L. (2014). Surgical management of gastro-oesophageal reflux disease (GORD) in adults: a systematic review and network meta-analysis. PROSPERO CRD42014010074. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010074

Amer, M.A., Smith, M.D., Herbison, G.P., Plank, L.D., and McCall, J.L. (2017). Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. Br J Surg *104*, 187-197.

Amer, M.A., Smith, M.D., Khoo, C.H., Herbison, G.P., and McCall, J.L. (2018). Network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults. Br J Surg *105*, 1398-1407.

American Society of Anesthesiologists, C. (2011). Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology *114*, 495-511.

An, G.Q., Zhao, X.L., Gao, Y.C., Wang, G.Y., and Yu, Y.M. (2008). Effects of preoperative carbohydrate loading on the changes in serum tumor necrosis factor receptors 1 and 2 and insulin resistance in patients of colon carcinoma. Nat Med J China *88*, 2041-2044.

Anvari, M., Allen, C., Marshall, J., Armstrong, D., Goeree, R., Ungar, W., and Goldsmith, C. (2006). A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: one-year follow-up. Surg Innov *13*, 238–249.

Anvari, M., Allen, C., Marshall, J., Armstrong, D., Goeree, R., Ungar, W., and Goldsmith, C. (2011). A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the

treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. Surg Endosc *25*, 2547–2554.

Aronsson, A., Al-Ani, N.A., Brismar, K., and Hedstrom, M. (2009). A carbohydrate-rich drink shortly before surgery affected IGF-I bioavailability after a total hip replacement. A double-blind placebo controlled study on 29 patients. Aging Clin Exp Res *21*, 97-101.

Asakura, A., Mihara, T., and Goto, T. (2015). The Effect of Preoperative Oral Carbohydrate or Oral Rehydration Solution on Postoperative Quality of Recovery: A Randomized, Controlled Clinical Trial. PLoS ONE *10*, e0133309.

Ashrafian, H., Rao, C., Darzi, A., and Athanasiou, T. (2009). Benchmarking in surgical research. Lancet *374*, 1045-1047.

Awad, S., Varadhan, K.K., Ljungqvist, O., and Lobo, D.N. (2013). A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin Nutr *32*, 34-44.

Aye, R.W., Swanstrom, L.L., Kapur, S., Buduhan, G., Dunst, C.M., Knight, A., Malmgren, J.A., and Louie, B.E. (2012). A randomized multiinstitution comparison of the laparoscopic Nissen and Hill repairs. Ann Thorac Surg *94*, 951–958.

Bafeta, A., Trinquart, L., Seror, R., and Ravaud, P. (2014). Reporting of results from network meta-analyses: methodological systematic review. BMJ *348*, g1741.

Baigrie, R.J., Cullis, S.N.R., Ndhluni, A.J., and Cariem, A. (2005). Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Brit J Surg *92*, 819–823.

Baker, S.G., and Kramer, B.S. (2002). The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? BMC Med Res Methodol *2*, 13.

Barkun, J.S., Aronson, J.K., Feldman, L.S., Maddern, G.J., Strasberg, S.M., Balliol, C., Altman, D.G., Barkun, J.S., Blazeby, J.M., Boutron, I.C., *et al.* (2009). Evaluation and stages of surgical innovations. Lancet *374*, 1089-1096.

Baxter, S.T., Walker, S.J., and Sutton, R. (1996). Randomised controlled trial of Nissen versus Lind fundoplication: results at ten years follow-up. In Recent advances in diseases of the esophagus, A. Peracchia, R. Rosati, L. Bonavina, U. Fumagalli, S. Bona, and B. Chella, eds. (Bologne: Monduzzi Editore Spa), 675–676.

Beecher, H.K. (1955). The powerful placebo. J Am Med Assoc *159*, 1602-1606.

Bernstein, M.H., and Brown, W.A. (2017). The placebo effect in psychiatric practice. Curr Psychiatr *16*, 29-34.

Bingener, J., Skaran, P., McConico, A., Novotny, P., Wettstein, P., Sletten, D.M., Park, M., Low, P., and Sloan, J. (2015). A Double-Blinded Randomized Trial to Compare the Effectiveness of Minimally Invasive Procedures Using Patient-Reported Outcomes. J Am Coll Surg *221*, 111-121.

Bisgaard, T., Kristiansen, V.B., Hjortso, N.C., Jacobsen, L.S., Rosenberg, J., and Kehlet, H. (2004). Randomized clinical trial comparing an oral carbohydrate beverage with placebo before laparoscopic cholecystectomy. Br J Surg *91*, 151-158.

Blomqvist, A., Dalenback, J., Hagedorn, C., Lonroth, H., Hyltander, A., and Lundell, L. (2000). Impact of complete gastric fundus mobilization on outcome after laparoscopic total fundoplication. J Gastrointest Surg *4*, 493–500.

BMJ (2017). Study design search filters. http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html Accessed October 4, 2017

Booth, M.I., Stratford, J., Jones, L., and Dehn, T.C. (2008). Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg *95*, 57-63.

Bouillot, J.L., Alamowitch, B., Aouad, K., Gasne, P., Gilbert, T., Bloch, F., and et, a.l. (1999). [Laparoscopy cure of gastro-oesophageal reflux. Nissen versus Toupet: a prospective randomized study in 50 patients]. Ann Chir, 669.

Boutron, I., Tubach, F., Giraudeau, B., and Ravaud, P. (2004). Blinding was judged more difficult to achieve and maintain in nonpharmacologic than pharmacologic trials. J Clin Epidemiol *57*, 543-550.

Bracale, U., Melillo, P., Pignata, G., Di Salvo, E., Rovani, M., Merola, G., and Pecchia, L. (2012). Which is the best laparoscopic approach for inguinal hernia repair: TEP or TAPP? A systematic review of the literature with a network meta-analysis. Surg Endosc *26*, 3355-3366.

Brady, M., Kinn, S., and Stuart, P. (2003). Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Sys Rev, CD004423.

Braga, M., Bissolati, M., Rocchetti, S., Beneduce, A., Pecorelli, N., and Di Carlo, V. (2012). Oral preoperative antioxidants in pancreatic surgery: a double-blind, randomized, clinical trial. Nutrition *28*, 160-164.

Brennan, M.F. (2008). Is nil per os still appropriate for patients undergoing upper gastrointestinal surgery? Nat Clin Pract Gastroenterol Hepatol *5*, 660-661.

Breuer, J.P., von Dossow, V., von Heymann, C., Griesbach, M., von Schickfus, M., Mackh, E., Hacker, C., Elgeti, U., Konertz, W., Wernecke, K.D., *et al.* (2006). Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery. Anesth Analgesia *103*, 1099-1108.

Broeders, J., Mauritz, F.A., Ali, U.A., Draaisma, W.A., Ruurda, J.P., Gooszen, H.G., Smout, A., Broeders, I., and Hazebroek, E.J. (2010). Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Brit J Surg *97*, 1318-1330.

Broeders, J.A., Roks, D.J., Ahmed Ali, U., Draaisma, W.A., Smout, A.J., and Hazebroek, E.J. (2011). Laparoscopic anterior versus posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. Ann Surg *254*, 39–47.

Broeders, J.A., Roks, D.J., Ahmed Ali, U., Watson, D.I., Baigrie, R.J., Cao, Z., Hartmann, J., and Maddern, G.J. (2013). Laparoscopic anterior 180-degree versus Nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. Ann Surg *257*, 850–859.

Broeders, J.A., Roks, D.J., Jamieson, G.G., Devitt, P.G., Baigrie, R.J., and Watson, D.I. (2012). Five-year outcome after laparoscopic anterior partial versus Nissen fundoplication: four randomized trials. Ann Surg *255*, 637–642.

Brown, S., Hutton, B., Clifford, T., Coyle, D., Grima, D., Wells, G., and Cameron, C. (2014). A Microsoft-Excel-based tool for running and critically appraising network meta-analyses – an overview and application of NetMetaXL. Syst Rev *3*, 110.

Cai, W., Watson, D.I., Lally, C.J., Devitt, P.G., Game, P.A., and Jamieson, G.G. (2008). Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180 degrees partial fundoplication. Brit J Surg *95*, 1501–1505.

Caldwell, D.M., Ades, A.E., and Higgins, J.P. (2005). Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ *331*, 897–900.

Caldwell, D.M., Welton, N.J., Dias, S., and Ades, A.E. (2012). Selecting the best scale for measuring treatment effect in a network meta-analysis: a case study in childhood nocturnal enuresis. Res Syn Meth *3*, 126-141.

Canbay, O., Adar, S., Karagoz, A.H., Celebi, N., and Bilen, C.Y. (2014). Effect of preoperative consumption of high carbohydrate drink (Pre-Op (A (R))) on postoperative metabolic stress reaction in patients undergoing radical prostatectomy. Int Urol Neph *46*, 1329-1333.

Cao, Z., Cai, W., Qin, M., Zhao, H., Yue, P., and Li, Y. (2012). Randomized clinical trial of laparoscopic anterior 180 degrees partial versus 360 degrees Nissen fundoplication: 5 year results. Dis Esophagus *25*, 114–120.

Carmichael, J.C., Keller, D.S., Baldini, G., Bordeianou, L., Weiss, E., Lee, L., Boutros, M., McClane, J., Feldman, L.S., and Steele, S.R. (2017). Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery From the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Dis Colon Rectum *60*, 761-784.

Cerantola, Y., Valerio, M., Persson, B., Jichlinski, P., Ljungqvist, O., Hubner, M., Kassouf, W., Muller, S., Baldini, G., Carli, F., *et al.* (2013). Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS) society recommendations. Clin Nut *32*, 879-887.

Chaimani, A., Higgins, J.P., Mavridis, D., Spyridonos, P., and Salanti, G. (2013). Graphical tools for network meta-analysis in STATA. PLoS ONE *8*, e76654.

Chaimani, A., and Salanti, G. (2012). Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Res Syn Meth *3*, 161-176.

Chaimani, A., and Salanti, G. (2015). Visualizing assumptions and results in network meta-analysis: The network graphs package. Stata J *15*, 905-950.

Chaimani, A., Salanti, G., Leucht, S., Geddes, J.R., and Cipriani, A. (2017). Common pitfalls and mistakes in the set-up, analysis and interpretation of results in network meta-analysis: what clinicians should look for in a published article. Evid Based Ment Health *80*, 88-94.

Chalmers, I. (1990). Underreporting research is scientific misconduct. JAMA *263*, 1405-1408.

Chalmers, I. (1997). What is the prior probability of a proposed new treatment being superior to established treatments? BMJ *314*, 74-75.

Chalmers, I., Glasziou, P., and Godlee, F. (2013). All trials must be registered and the results published. BMJ *346*, f105.

Chalmers, I., and Matthews, R. (2006). What are the implications of optimism bias in clinical research? Lancet *367*, 449-450.

Chaudhry, H., Foote, C.J., Guyatt, G., Thabane, L., Furukawa, T.A., Petrisor, B., and Bhandari, M. (2015). Network Meta-analysis: Users' Guide for Surgeons: Part II - Certainty. Clin Orthop Relat Res *473*, 2172-2178.

Chen, J., Cheng, L., Xie, Z., and Li, Z. (2014). The effect of the preoperative oral intake of 10% glucose solution on postoperative insulin resistance in patients undergoing gastric cancer resection. J Pract Med *30*, 1562-1565.

Chen, J., Cheng, L., Xie, Z., and Li, Z. (2015). [Impact of preoperative oral liquid carbohydrate on postoperative insulin resistance in gastric cancer patients and its associated study]. Zhonghua Wei Chang Wai Ke Za Zhi *18*, 1256-1260.

Chrysos, E., Athanasakis, E., Pechlivanides, G., Tzortzinis, A., Mantides, A., and Xynos, E. (2004). The effect of total and anterior partial fundoplication on antireflux mechanisms of the gastroesophageal junction. Am J Surg *188*, 39–44.

Chrysos, E., Tsiaoussis, J., Zoras, O.J., Athanasakis, E., Mantides, A., Katsamouris, A., and Xynos, E. (2003). Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? J Am Coll Surgeons *197*, 8–15.

Chrysos, E., Tzortzinis, A., Tsiaoussis, J., Athanasakis, H., Vasssilakis, J.S., and Xynos, E. (2001). Prospective randomized trial comparing Nissen to Nissen-Rossetti technique for laparoscopic fundoplication. Am J Surg *182*, 215–221.

Cipriani, A., Barbui, C., Salanti, G., Rendell, J., Brown, R., Stockton, S., Purgato, M., Spineli, L.M., Goodwin, G.M., and Geddes, J.R. (2011). Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet *378*, 1306-1315.

Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., *et al.* (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet *391*, 1357-1366.

Cipriani, A., Williams, T., Nikolakopoulou, A., Salanti, G., Chaimani, A., Ipser, J., Cowen, P.J., Geddes, J.R., and Stein, D.J. (2018). Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychol Med *48*, 1975-1984.

Cipriani, A., Zhou, X., Del Giovane, C., Hetrick, S.E., Qin, B., Whittington, C., Coghill, D., Zhang, Y., Hazell, P., Leucht, S., *et al.* (2016). Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. Lancet *388*, 881-890.

Clegg, A.J., Loveman, E., Gospodarevskaya, E., Harris, P., Bird, A., Bryant, J., Scott, D.A., Davidson, P., Little, P., and Coppin, R. (2010). The safety and effectiveness of different methods of earwax removal: a systematic review and economic evaluation. Health Technol Assess *14*, 1-192.

Cobb, L.A., Thomas, G.I., Dillard, D.H., Merendino, K.A., and Bruce, R.A. (1959). An evaluation of internal-mammary-artery ligation by a double-blind technic. N Engl J Med *260*, 1115-1118.

Cochrane (2013). Data extraction form for RCTs, Version 2 (The Cochrane Collaboration). https://training.cochrane.org/sites/training.cochrane.org/files/public/uploads/resources/downloadable_resources/English/Collecting%20data%20-%20form%20for%20RCTs%20only.doc Accessed October 15, 2015

Cochrane, A.L. (1972). Effectiveness and efficiency: random reflections on health services (London: Nuffield Provincial Hospitals Trust).

Cochrane.org (2018). About Cochrane. http://www.cochrane.org/about-us Accessed February 25, 2018

Cochrane.org (2018). A network meta-analysis toolkit. https://methods.cochrane.org/cmi/network-meta-analysis-toolkit Accessed August 11, 2018

Cotton, P.B., Durkalski, V., Romagnuolo, J., Pauls, Q., Fogel, E., Tarnasky, P., Aliperti, G., Freeman, M., Kozarek, R., Jamidar, P., *et al.* (2014). Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA *311*, 2101-2109.

Crowley, P. (1981). Corticosteroids in pregnancy: the benefits outweight the costs. Journal of Obstetrics and Gynaecology *1*, 147-150.

Csendes, A., Burdiles, P., Korn, O., Braghetto, I., Huertas, C., and Rojas, J. (2000). Late results of a randomized clinical trial comparing total fundoplication versus calibration of the cardia with posterior gastropexy. Brit J Surg *87*, 289–297.

Cunningham, J.E. (2011). Intention-to-treat analysis: the parachute revisited. ANZ J Surg *81*, 920-922.

Cuschieri, A. (1989). The laparoscopic revolution--walk carefully before we run. J R Coll Surg Edinb *34*, 295.

Cuschieri, A., Berci, G., and McSherry, C.K. (1990). Laparoscopic cholecystectomy. Am J Surg *159*, 273.

Dakkak, M., and Bennett, J.R. (1992). A new dysphagia score with objective validation. J Clin Gastroenterol *14*, 99–100.

Daud, W.N., Thompson, S.K., Jamieson, G.G., Devitt, P.G., Martin, I.J., and Watson, D.I. (2015). Randomized controlled trial of laparoscopic anterior 180 degree partial versus posterior 270 degree partial fundoplication. ANZ J Surg *85*, 668–672.

Davies, C., Radua, J., Cipriani, A., Stahl, D., Provenzani, U., McGuire, P., and Fusar-Poli, P. (2018). Efficacy and Acceptability of Interventions for Attenuated Positive Psychotic Symptoms in Individuals at Clinical High Risk of Psychosis: A Network Meta-Analysis. Front Psych *9*, 187.

Day, S.J., and Altman, D.G. (2000). Statistics notes: blinding in clinical trials and other studies. BMJ *321*, 504.

Dechartres, A., Trinquart, L., Boutron, I., and Ravaud, P. (2013). Influence of trial sample size on treatment effect estimates: meta-epidemiological study. BMJ *346*, f2304.

de Craen, A.J., Kaptchuk, T.J., Tijssen, J.G., and Kleijnen, J. (1999). Placebos and placebo effects in medicine: historical overview. J R Soc Med *92*, 511-515.

Demeester, T.R., Johnson, L.F., and Kent, A.H. (1974). Evaluation of current operations for the prevention of gastroesophageal reflux. Ann Surg *180*, 511–525.

Dent, J., El-Serag, H.B., Wallander, M.A., and Johansson, S. (2005). Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut *54*, 710–717.

Detsky, A.S., Naylor, C.D., O'Rourke, K., McGeer, A.J., and L'Abbe, K.A. (1992). Incorporating variations in the quality of individual randomized trials into meta-analysis. J Clin Epidemiol *45*, 255-265.

Devereaux, P.J., Manns, B.J., Ghali, W.A., Quan, H., Lacchetti, C., Montori, V.M., Bhandari, M., and Guyatt, G.H. (2001). Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. JAMA *285*, 2000-2003.

Dias, S., Welton, N.J., Caldwell, D.M., and Ades, A.E. (2010). Checking consistency in mixed treatment comparison meta-analysis. Stat Med *29*, 932–944.

Dias, S., Welton, N.J., Sutton, A.J., and Ades, A.E. (2012). NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making. http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/ Accessed October 4, 2017

Dimond, E.G., Kittle, C.F., and Crockett, J.E. (1960). Comparison of internal mammary artery ligation and sham operation for angina pectoris. Am J Cardiol *5*, 483-486.

Djerf, P., Montgomery, A., Hallerback, B., Hakansson, H.O., and Johnsson, F. (2016). One- and ten-year outcome of laparoscopic anterior 120 degrees versus total fundoplication: a double-blind, randomized multicenter study. Surg Endosc *30*, 168–177.

Dock-Nascimento, D.B., de Aguilar-Nascimento, J.E., Magalhaes Faria, M.S., Caporossi, C., Slhessarenko, N., and Waitzberg, D.L. (2012). Evaluation of the effects of a preoperative 2-hour fast with maltodextrine and glutamine on insulin resistance, acute-phase response, nitrogen balance, and serum glutathione after laparoscopic cholecystectomy: a controlled randomized trial. J Parenter Enteral Nutr *36*, 43-52.

Donegan, S., Williamson, P., Gamble, C., and Tudur-Smith, C. (2010). Indirect comparisons: a review of reporting and methodological quality. PLoS One *5*, e11054.

Efthimiou, O., Debray, T.P., van Valkenhoef, G., Trelle, S., Panayidou, K., Moons, K.G., Reitsma, J.B., Shang, A., Salanti, G., and GetReal Methods Review, G. (2016). GetReal in network meta-analysis: a review of the methodology. Res Syn Meth *7*, 236-263.

Engstrom, C., Lonroth, H., Mardani, J., and Lundell, L. (2007). An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg *31*, 1221–1227.

Ergina, P.L., Cook, J.A., Blazeby, J.M., Boutron, I., Clavien, P.A., Reeves, B.C., Seiler, C.M., Balliol, C., Altman, D.G., Aronson, J.K., *et al.* (2009). Challenges in evaluating surgical innovation. Lancet *374*, 1097-1104.

Eyre-Brook, I.A., Codling, B.W., and Gear, M.W. (1993). Results of a prospective randomized trial of the Angelchik prosthesis and of a consecutive series of 119 patients. Brit J Surg *80*, 602–604.

Farah, J.F.D., Del Grande, J.C., Goldenberg, A., Martinez, J.C., Lupinacci, R.A., and Matone, J. (2007). Randomized trial of total fundoplication and fundal mobilization with or without division of short gastric vessels. A short-term clinical evaluation. Acta Cir Bras *22*, 422–429.

Faria, M.S., de Aguilar-Nascimento, J.E., Pimenta, O.S., Alvarenga, L.C., Jr., Dock-Nascimento, D.B., and Slhessarenko, N. (2009). Preoperative fasting of 2 hours minimizes insulin resistance and organic response to trauma after video-cholecystectomy: a randomized, controlled, clinical trial. World J Surg *33*, 1158-1164.

Faria, R., Bojke, L., Epstein, D., Corbacho, B., and Sculpher, M. (2013). Cost-effectiveness of laparoscopic fundoplication versus continued medical management for the treatment of gastro-oesophageal reflux disease based on long-term follow-up of the REFLUX trial. Brit J Surg *100*, 1205–1213.

Feguri, G.R., Lima, P.R., Lopes, A.M., Roledo, A., Marchese, M., Trevisan, M., Ahmad, H., Freitas, B.B., and Aguilar-Nascimento, J.E. (2012). Clinical and metabolic results of fasting abbreviation with carbohydrates in coronary artery bypass graft surgery. Rev Bras Cir Cardiovasc *27*, 7-17.

Fergusson, D., Glass, K.C., Waring, D., and Shapiro, S. (2004). Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. BMJ *328*, 432.

Ferulano, G.P., La Manna, S., Dilillo, S., Forgione, A., Vanni, L., Brunaccino, R., Lionetti, R., and D'Ambra, M. (2000). Laparoscopic partial posterior vs. total fundoplication in gastro-oesophageal reflux disease (GERD) with oesophageal dismotility, short term results of a prospective study.

Feys, F., Bekkering, G.E., Singh, K., and Devroey, D. (2014). Do randomized clinical trials with inadequate blinding report enhanced placebo effects for intervention groups and nocebo effects for placebo groups? Syst Rev *3*, 14.

Fowler, H.W., and Fowler, F.G. (2011). The concise Oxford dictionary of current English: 1911 first edition, 100th Anniversary edn (Oxford; New York, NY: Oxford University Press).

Franchini, A.J., Dias, S., Ades, A.E., Jansen, J.P., and Welton, N.J. (2012). Accounting for correlation in network meta-analysis with multi-arm trials. Res Syn Meth *3*, 142-160.

Freed, C.R., Greene, P.E., Breeze, R.E., Tsai, W.Y., DuMouchel, W., Kao, R., Dillon, S., Winfield, H., Culver, S., Trojanowski, J.Q., *et al.* (2001). Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med *344*, 710-719.

Fry, L.C., Monkemuller, K., and Malfertheiner, P. (2007). Systematic review: endoluminal therapy for gastro-oesophageal reflux disease: evidence from clinical trials. Eur J Gastroenterol Hepatol *19*, 1125-1139.
Fuchs, K.H., Babic, B., Breithaupt, W., Dallemagne, B., Fingerhut, A., Furnee, E., Granderath, F., Horvath, P., Kardos, P., Pointner, R., *et al.* (2014). EAES recommendations for the management of gastroesophageal reflux disease. Surg Endosc *28*, 1753–1773.

Galmiche, J.P., Hatlebakk, J., Attwood, S., Ell, C., Fiocca, R., Eklund, S., Langstrom, G., Lind, T., Lundell, L., and Collaborators, L.T. (2011). Laparoscopic antireflux surgery vs Esomeprazole treatment for Chronic GERD - the LOTUS randomized clinical trial. JAMA *305*, 1969–1977.

Gattellari, M., Ward, J.E., and Solomon, M.J. (2001). Randomized, controlled trials in surgery: perceived barriers and attitudes of Australian colorectal surgeons. Dis Colon Rectum *44*, 1413-1420.

Gear, M.W., Gillison, E.W., and Dowling, B.L. (1984). Randomized prospective trial of the Angelchik anti-reflux prosthesis. Brit J Surg *71*, 681–683.

Glass, G.V. (1976). Primary, secondary, and meta-analysis of research. Educational Researcher *5*, 3-8.

Goeree, R., Hopkins, R., Marshall, J.K., Armstrong, D., Ungar, W.J., Goldsmith, C., Allen, C., and Anvari, M. (2011). Cost-utility of laparoscopic Nissen fundoplication versus proton pump inhibitors for chronic and controlled gastroesophageal reflux disease: a 3-year prospective randomized controlled trial and economic evaluation. Value Health *14*, 263–273.

Goligher, J.C., Pulvertaft, C.N., and Watkinson, G. (1964). Controlled Trial of Vagotomy and Gastro-Enterostomy, Vagotomy and Antrectomy, and Subtotal Gastrectomy in Elective Treatment of Duodenal Ulcer: Interim Report. Br Med J *1*, 455-460.

Goodman, S., and Dickersin, K. (2011). Metabias: a challenge for comparative effectiveness research. Ann Intern Med *155*, 61-62.

Gouvas, N., Tan, E., Windsor, A., Xynos, E., and Tekkis, P.P. (2009). Fast-track vs standard care in colorectal surgery: a meta-analysis update. Int J Colorect Dis *24*, 1119-1131.

Grainger, S., Smith, M.D., McCall, J.L., and Amer, M.A. (2018). Bariatric surgery in adults: a systematic review and network meta-analysis. PROSPERO CRD42018088266. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018088266

Granderath, F.A., Kamolz, T., Granderath, U.M., and Pointner, R. (2007). Gas-related symptoms after laparoscopic 360 degrees Nissen or 270 degrees Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. Digest Liver Dis *39*, 312–318.

Granderath, F.A., Schweiger, U.M., Kamolz, T., Asche, K.U., and Pointner, R. (2005). Laparoscopic Nissen fundoplication with prosthetic hiatal closure reduces postoperative intrathoracic wrap herniation - preliminary results of a prospective randomized functional and clinical study. Arch Surg *140*, 40–48.

Grant, A.M., Cotton, S.C., Boachie, C., Ramsay, C.R., Krukowski, Z.H., Heading, R.C., Campbell, M.K., and Group, R.T. (2013). Minimal access surgery compared with medical management for gastro-oesophageal reflux disease: five year follow-up of a randomised controlled trial (REFLUX). BMJ *346*, f1908.

Green, S., and McDonald, S. (2005). Cochrane Collaboration: more than systematic reviews? Intern Med J *35*, 3-4.

Guerin, E., Betroune, K., Closset, J., Mehdi, A., Lefebvre, J.C., Houben, J.J., Gelin, M., Vaneukem, P., and El Nakadi, I. (2007). Nissen versus Toupet fundoplication: results of a randomized and multicenter trial. Surg Endosc *21*, 1985–1990.

Gustafsson, U.O., Scott, M.J., Schwenk, W., Demartines, N., Roulin, D., Francis, N., McNaught, C.E., Macfie, J., Liberman, A.S., Soop, M., *et al.* (2013). Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS()) Society recommendations. World Journal of Surgery *37*, 259-284.

Haahr, M.T., and Hrobjartsson, A. (2006). Who is blinded in randomized clinical trials? A study of 200 trials and a survey of authors. Clin Trials *3*, 360-365.

Hagedorn, C., Jonson, C., Lonroth, H., Ruth, M., Thune, A., and Lundell, L. (2003). Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication - results of a randomized, controlled clinical trial. Ann Surg *238*, 189–196.

Hagedorn, C., Lonroth, H., Rydberg, L., Ruth, M., and Lundell, L. (2002). Long-term efficacy of total (Nissen-Rossetti) and posterior partial (Toupet) fundoplication: results of a randomized clinical trial. J Gastrointest Surg *6*, 540–545.

Hall, J.C. (2010). How to dissect surgical journals: V - Patients. ANZ J Surg *80*, 846-851.

Harbord, R.M., and Higgins, J.P.T. (2008). Meta-regression in Stata. Stata J *8*, 493-519.

Harris, R.J., Bradburn, M.J., Deeks, J.J., Harbord, R.M., Altman, D.G., and Sterne, J.A. (2008). metan: fixed- and random-effects meta-analysis. Stata J *8*, 3-28.

Harsten, A., Hjartarson, H., and Toksvig-Larsen, S. (2012). Total hip arthroplasty and perioperative oral carbohydrate treatment: a randomised, double-blind, controlled trial. Eur J Anaesthesiol *29*, 271-274.

Hatlebakk, J.G., Zerbib, F., Bruley des Varannes, S., Attwood, S.E., Ell, C., Fiocca, R., Galmiche, J.P., Eklund, S., Langstrom, G., Lind, T., *et al.* (2016). Gastroesophageal acid reflux control 5 years after antireflux surgery, compared with long-term Esomeprazole therapy. Clin Gastroenterol H *14*, 678–685 e673.

Hausel, J., Nygren, J., Thorell, A., Lagerkranser, M., and Ljungqvist, O. (2005). Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. Br J Surg *92*, 415-421.

Henriksen, M.G., Hessov, I., Dela, F., Hansen, H.V., Haraldsted, V., and Rodt, S.A. (2003). Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. Acta Anaesthesiol Scand *47*, 191-199.

Heres, S., Davis, J., Maino, K., Jetzinger, E., Kissling, W., and Leucht, S. (2006). Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry *163*, 185-194.

Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., *et al.* (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ *343*, d5928.

Higgins, J.P., and Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions, 5.1.0 (The Cochrane Collaboration) Available from https://www.cochrane-handbook.org

Higgins, J.P., Jackson, D., Barrett, J.K., Lu, G., Ades, A.E., and White, I.R. (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Syn Meth *3*, 98-110.

Higgins, J.P., and Welton, N.J. (2015). Network meta-analysis: a norm for comparative effectiveness? Lancet *386*, 628-630.

Hill, A.D., Walsh, T.N., Bolger, C.M., Byrne, P.J., and Hennessy, T.P. (1994). Randomized controlled trial comparing Nissen fundoplication and the Angelchik prosthesis. Brit J Surg *81*, 72–74.

Hill, C.L., LaValley, M.P., and Felson, D.T. (2002). Discrepancy between published report and actual conduct of randomized clinical trials. J Clin Epidemiol *55*, 783-786.

Hogan, W.J. (2006). Clinical trials evaluating endoscopic GERD treatments: is it time for a moratorium on the clinical use of these procedures? Am J Gastroenterol *101*, 437-439.

Horton, R. (1996). Surgical research or comic opera: questions, but few answers. Lancet *347*, 984-985.
Howes, N., Chagla, L., Thorpe, M., and McCulloch, P. (1997). Surgical practice is evidence based. Br J Surg *84*, 1220-1223.

Hozo, S.P., Djulbegovic, B., and Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol *5*, 13.

Hrobjartsson, A., Thomsen, A.S., Emanuelsson, F., Tendal, B., Hilden, J., Boutron, I., Ravaud, P., and Brorson, S. (2012). Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. BMJ *344*, e1119.

Hrobjartsson, A., Thomsen, A.S., Emanuelsson, F., Tendal, B., Hilden, J., Boutron, I., Ravaud, P., and Brorson, S. (2013). Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. CMAJ *185*, E201-211.

Hrobjartsson, A., Thomsen, A.S., Emanuelsson, F., Tendal, B., Rasmussen, J.V., Hilden, J., Boutron, I., Ravaud, P., and Brorson, S. (2014). Observer bias in randomized clinical trials with time-to-event outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. Int J Epidemiol *43*, 937-948.

Hutton, B., Salanti, G., Caldwell, D.M., Chaimani, A., Schmid, C.H., Cameron, C., Ioannidis, J.P., Straus, S., Thorlund, K., Jansen, J.P., *et al.* (2015). The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med *162*, 777–784.

Hutton, B., Salanti, G., Chaimani, A., Caldwell, D.M., Schmid, C., Thorlund, K., Mills, E., Catala-Lopez, F., Turner, L., Altman, D.G., *et al.* (2014). The quality of reporting methods and results in network meta-analyses: an overview of reviews and suggestions for improvement. PLoS One *9*, e92508.

Itou, K., Fukuyama, T., Sasabuchi, Y., Yasuda, H., Suzuki, N., Hinenoya, H., Kim, C., Sanui, M., Taniguchi, H., Miyao, H., *et al.* (2012). Safety and efficacy of oral rehydration therapy until 2 h before surgery: a multicenter randomized controlled trial. J Anesth *26*, 20-27.

Jack, W.J., Chetty, U., and Rodger, A. (1990). Recruitment to a prospective breast conservation trial: why are so few patients randomised? BMJ *301*, 83-85.

Jackson, J.L., Kuriyama, A., Anton, A., Choi, A., Fournier, J.P., Geier, A.K., Jacquerioz, F., Kogan, D., Scholcoff, C., and Sun, R. (2019). The Accuracy of Google Translate for Abstracting Data From Non-English-Language Trials for Systematic Reviews. Ann Intern Med.

Jackson, R. (2018). Rapid appraisal of clinical studies to inform clinical decision making. Paper presented at: Planning for Change: The 2018 Annual Surgical Meeting of the New Zealand Chapter of the Royal Australasian College of Surgeons (Queenstown, New Zealand).

Jansen, J.P., Crawford, B., Bergman, G., and Stam, W. (2008). Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health *11*, 956-964.

Jarvela, K., Maaranen, P., and Sisto, T. (2008). Pre-operative oral carbohydrate treatment before coronary artery bypass surgery. Acta Anaesthesiol Scand *52*, 793-797.

Juni, P., Altman, D.G., and Egger, M. (2001). Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ *323*, 42-46.

Kaptchuk, T.J., Goldman, P., Stone, D.A., and Stason, W.B. (2000). Do medical devices have enhanced placebo effects? J Clin Epidemiol *53*, 786-792.

Karanicolas, P.J., Bhandari, M., Taromi, B., Akl, E.A., Bassler, D., Alonso-Coello, P., Rigau, D., Bryant, D., Smith, S.E., Walter, S.D., *et al.* (2008). Blinding of outcomes in trials of orthopaedic trauma: an opportunity to enhance the validity of clinical trials. J Bone Joint Surg Am *90*, 1026-1033.

Karlsson, A., Wendel, K., Polits, S., Gislason, H., and Hedenbro, J.L. (2016). Preoperative Nutrition and Postoperative Discomfort in an ERAS Setting: A Randomized Study in Gastric Bypass Surgery. Obesity Surg *26*, 743-748.

Kaska, M., Grosmanova, T., Havel, E., Hyspler, R., Petrova, Z., Brtko, M., Bares, P., Bares, D., Schusterova, B., Pyszkova, L., *et al.* (2010). The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery--a randomized controlled trial. Wien Klin Wochenschr *122*, 23-30.

Kenny, S.E., Shankar, K.R., Rintala, R., Lamont, G.L., and Lloyd, D.A. (1997). Evidence-based surgery: interventions in a regional paediatric surgical unit. Arch Dis Child *76*, 50-53.

Keus, F., de Jong, J.A., Gooszen, H.G., and van Laarhoven, C.J. (2006). Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev, CD006231.

Khan, M., Smythe, A., Globe, J., Stoddard, C.J., and Ackroyd, R. (2010). Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. ANZ J Surg *80*, 500–505.

Khan, M.A., Smythe, A., Globe, J., Stoddard, C.J., and Ackroyd, R. (2009). Randomized controlled trial of laparoscopic Nissen versus Lind fundoplication for gastro-oesophageal reflux disease. Scand J Gastroenterol *44*, 269–275.

Kingston, R., Barry, M., Tierney, S., Drumm, J., and Grace, P. (2001). Treatment of surgical patients is evidence-based. Eur J Surg *167*, 324-330.

Kmiot, W.A., Kirby, R.M., Akinola, D., and Temple, J.G. (1991). Prospective randomized trial of Nissen fundoplication and Angelchik prosthesis in the surgical treatment of medically refractory gastro-oesophageal reflux disease. Brit J Surg *78*, 1181–1184.

Koch, O.O., Kaindlstorfer, A., Antoniou, S.A., Luketina, R.R., Emmanuel, K., and Pointner, R. (2013). Comparison of results from a randomized trial 1 year after laparoscopic Nissen and Toupet fundoplications. Surg Endosc *27*, 2383–2390.

Kosek, V., Wykypiel, H., Weiss, H., Holler, E., Wetscher, G., Margreiter, R., and Klaus, A. (2009). Division of the short gastric vessels during laparoscopic Nissen fundoplication: clinical and functional outcome during long-term follow-up in a prospectively randomized trial. Surg Endosc *23*, 2208–2213.
Lancet (2009). Surgical research: the reality and the IDEAL. Lancet *374*, 1037.

Lassen, K., Coolsen, M.M., Slim, K., Carli, F., de Aguilar-Nascimento, J.E., Schafer, M., Parks, R.W., Fearon, K.C., Lobo, D.N., Demartines, N., *et al.* (2012). Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS) Society recommendations. Clinical Nutrition *31*, 817-830.

Lassen, K., Hannemann, P., Ljungqvist, O., Fearon, K., Dejong, C.H., von Meyenfeldt, M.F., Hausel, J., Nygren, J., Andersen, J., Revhaug, A., *et al.* (2005). Patterns in current perioperative practice: survey of colorectal surgeons in five northern European countries. BMJ *330*, 1420-1421.

Lau, J., Ioannidis, J.P., Terrin, N., Schmid, C.H., and Olkin, I. (2006). The case of the misleading funnel plot. BMJ *333*, 597-600.

Lauwick, S.M., Kaba, A., Maweja, S., Hamoir, E.E., and Joris, J.L. (2009). Effects of oral preoperative carbohydrate on early postoperative outcome after thyroidectomy. Acta Anaesthes Belgica *60*, 67-73.

Laws, H.L., Clements, R.H., and Swillie, C.M. (1997). A randomized, prospective comparison of the Nissen fundoplication versus the Toupet fundoplication for gastroesophageal reflux disease. Ann Surg *225*, 647–654.

Li, L., Wang, Z., Ying, X.J., Tian, J.H., Sun, T.T., Kang, Y., Zhang, P., Jing, Z., and Yang, K.H. (2012). Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis. Surgery Today *42*, 613-624.

Lidder, P., Thomas, S., Fleming, S., Hosie, K., Shaw, S., and Lewis, S. (2013). A randomized placebo controlled trial of preoperative carbohydrate drinks and early postoperative nutritional supplement drinks in colorectal surgery. Colorectal Dis *15*, 737-745.

Liggins, G.C., and Howie, R.N. (1972). A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics *50*, 515-525.

Livingston, K.E. (1953). Cingulate cortex isolation for the treatment of psychoses and psychoneuroses. Res Publ Assoc Res Nerv Ment Dis *31*, 374-378.

Ljunggren, S., and Hahn, R.G. (2012). Oral nutrition or water loading before hip replacement surgery; a randomized clinical trial. Trials *13*, 97.

Ljunggren, S., Hahn, R.G., and Nystrom, T. (2014). Insulin sensitivity and beta-cell function after carbohydrate oral loading in hip replacement surgery: a double-blind, randomised controlled clinical trial. Clinical Nutrition *33*, 392-398.

Ljungqvist, O., Nygren, J., and Thorell, A. (2002). Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. Proc Nutr Soc *61*, 329-336.

Ljungqvist, O., Thorell, A., Gutniak, M., Haggmark, T., and Efendic, S. (1994). Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. J Am Coll Surg *178*, 329-336.

Lombardi, R. (2014). Designing randomized clinical trials in surgery. Br J Surg *101*, 293-295.

Love, J.W. (1975). Drugs and operations. Some important differences. JAMA *232*, 37-38.

Lu, G., and Ades, A.E. (2004). Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med *23*, 3105-3124.

Lubowski, D.Z. (2014). Enhanced Recovery After Surgery and laparoscopic colorectal surgery: where to now? ANZ Journal of Surgery *84*, 500-501.

Ludemann, R., Watson, D.I., Jamieson, G.G., Game, P.A., and Devitt, P.G. (2005). Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Brit J Surg *92*, 240–243.

Lumley, T. (2002). Network meta-analysis for indirect treatment comparisons. Stat Med *21*, 2313–2324.

Lundell, L., Abrahamsson, H., Ruth, M., Rydberg, L., Lonroth, H., and Olbe, L. (1996). Long-term results of a prospective randomized comparison of total fundic wrap (Nissen-Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux. Brit J Surg *83*, 830–835.

Lundell, L., Abrahamsson, H., Ruth, M., Sandberg, N., and Olbe, L.C. (1991). Lower esophageal sphincter characteristics and esophageal acid exposure following partial or 360 degrees fundoplication: results of a prospective, randomized, clinical study. World J Surg *15*, 115–121.

Luostarinen, M., Koskinen, M., Reinikainen, P., Karvonen, J., and Isolauri, J. (1995). Two antireflux operations: floppy versus standard Nissen fundoplication. Ann Med *27*, 199–205.

Luostarinen, M.E., and Isolauri, J.O. (1999). Randomized trial to study the effect of fundic mobilization on long-term results of Nissen fundoplication. Brit J Surg *86*, 614–618.

Luostarinen, M.E.S., Koskinen, M.O., and Isolauri, J.O. (1996). Effect of fundal mobilisation in Nissen-Rossetti fundoplication on oesophageal transit and dysphagia - a prospective, randomised trial. Eur J Surg *162*, 37–42.

Ma, S., Qian, B., Shang, L., Shi, R., and Zhang, G. (2012). A meta-analysis comparing laparoscopic partial versus Nissen fundoplication. ANZ J Surg *82*, 17–22.

Mackay, C., Wileman, S.M., Krukowski, Z.H., and Bruce, J. (2010). Laparoscopic fundoplication for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev *9*, CD008719.

Mahon, D., Rhodes, M., Decadt, B., Hindmarsh, A., Lowndes, R., Beckingham, I., Koo, B., and Newcombe, R.G. (2005). Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. Brit J Surg *92*, 695–699.

Mant, D. (1999). Can randomised trials inform clinical decisions about individual patients? Lancet *353*, 743-746.

Mardani, J., Lundell, L., Lonroth, H., Dalenback, J., and Engstrom, C. (2009). Ten-year results of a randomized clinical trial of laparoscopic total fundoplication with or without division of the short gastric vessels. Brit J Surg *96*, 61–65.

Martin, R.C., 2nd, Polk, H.C., Jr., and Jaques, D.P. (2003). Does additional surgical training increase participation in randomized controlled trials? Am J Surg *185*, 239-243.

Mathew, G., Watson, D.I., Myers, J.C., Holloway, R.H., and Jamieson, G.G. (1997). Oesophageal motility before and after laparoscopic Nissen fundoplication. Brit J Surg *84*, 1465–1469.

Mathur, S., Plank, L.D., McCall, J.L., Shapkov, P., McIlroy, K., Gillanders, L.K., Merrie, A.E., Torrie, J.J., Pugh, F., Koea, J.B., *et al.* (2010). Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. Br J Surg *97*, 485-494.

Mazaki, T., Ishii, Y., and Murai, I. (2015). Immunoenhancing enteral and parenteral nutrition for gastrointestinal surgery: a multiple-treatments meta-analysis. Ann Surg *261*, 662-669.

McCormack, K., Scott, N.W., Go, P.M., Ross, S., Grant, A.M., and Collaboration, E.U.H.T. (2003). Laparoscopic techniques versus open techniques for inguinal hernia repair. Cochrane Database Syst Rev, CD001785.

McCulloch, P., Altman, D.G., Campbell, W.B., Flum, D.R., Glasziou, P., Marshall, J.C., Nicholl, J., Balliol, C., Aronson, J.K., Barkun, J.S., *et al.* (2009). No surgical innovation without evaluation: the IDEAL recommendations. Lancet *374*, 1105-1112.

McCulloch, P., Taylor, I., Sasako, M., Lovett, B., and Griffin, D. (2002). Randomised trials in surgery: problems and possible solutions. BMJ *324*, 1448-1451.

McGauran, N., Wieseler, B., Kreis, J., Schuler, Y.B., Kolsch, H., and Kaiser, T. (2010). Reporting bias in medical research - a narrative review. Trials *11*, 37.

McRae, C., Cherin, E., Yamazaki, T.G., Diem, G., Vo, A.H., Russell, D., Ellgring, J.H., Fahn, S., Greene, P., Dillon, S., *et al.* (2004). Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. Arch Gen Psychiatry *61*, 412-420.

Meakins, J.L. (2006). Evidence-based surgery. Surg Clin North Am *86*, 1-16.

Meakins, J.L. (2009). Surgical research: act 3, answers. Lancet *374*, 1039-1040.

Mehta, S., Bennett, J., Mahon, D., and Rhodes, M. (2006). Prospective trial of laparoscopic Nissen fundoplication versus proton pump inhibitor therapy for gastro-oesophageal reflux disease: seven year follow up. Gastroenterology *130*, A861.

Meisner, M., Ernhofer, U., and Schmidt, J. (2008). [Liberalisation of preoperative fasting guidelines: effects on patient comfort and clinical practicability during elective laparoscopic surgery of the lower abdomen]. Zentralblatt Fur Chirurgie *133*, 479-485.

Melis, M., Karl, R.C., Wong, S.L., Brennan, M.F., Matthews, J.B., and Roggin, K.K. (2010). Evidence-based surgical practice in academic medical centers: consistently anecdotal? J Gastrointest Surg *14*, 904-909.

Memon, M.A., Subramanya, M.S., Hossain, M.B., Yunus, R.M., Khan, S., and Memon, B. (2015). Laparoscopic anterior versus posterior fundoplication for gastro-esophageal reflux disease: a meta-analysis and systematic review. World J Surg *39*, 981–996.

Mickevicius, A., Endzinas, Z., Kiudelis, M., Jonaitis, L., Kupcinskas, L., Maleckas, A., and Pundzius, J. (2008). Influence of wrap length on the effectiveness of Nissen and Toupet fundoplication: a prospective randomized study. Surg Endosc *22*, 2269–2276.

Mickevicius, A., Endzinas, Z., Kiudelis, M., Jonaitis, L., Kupcinskas, L., Pundzius, J., and Maleckas, A. (2013). Influence of wrap length on the effectiveness of Nissen and Toupet fundoplications: 5-year results of prospective, randomized study. Surg Endosc *27*, 986–991.

Mills, E.J., Thorlund, K., and Ioannidis, J.P. (2013). Demystifying trial networks and network meta-analysis. BMJ *346*, f2914.

Miura, T., Noma, H., Furukawa, T.A., Mitsuyasu, H., Tanaka, S., Stockton, S., Salanti, G., Motomura, K., Shimano-Katsuki, S., Leucht, S., *et al.* (2014). Comparative efficacy and tolerability of pharmacological

treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psych *1*, 351-359.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ *339*, b2535.

Moher, D., Pham, B., Jones, A., Cook, D.J., Jadad, A.R., Moher, M., Tugwell, P., and Klassen, T.P. (1998). Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet *352*, 609-613.

Montori, V.M., Bhandari, M., Devereaux, P.J., Manns, B.J., Ghali, W.A., and Guyatt, G.H. (2002). In the dark: the reporting of blinding status in randomized controlled trials. J Clin Epidemiol *55*, 787-790.

Mortensen, K., Nilsson, M., Slim, K., Schafer, M., Mariette, C., Braga, M., Carli, F., Demartines, N., Griffin, S.M., Lassen, K., *et al.* (2014). Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS) Society recommendations. Brit J Surg *101*, 1209-1229.

Mucio, M., Rojano, M., Herrera, J.J., Valdovinos, M.A., Cordova, J.A., Bravo, C., Dominguez, L., and Sanchez, O. (2012). Novel surgical concept in antireflux surgery: long-term outcomes comparing 3 different laparoscopic approaches. Surgery *151*, 84–93.

Muller-Stich, B.P., Linke, G.R., Senft, J., Achtstatter, V., Muller, P.C., Diener, M.K., Warschkow, R., Marra, F., Schmied, B.M., Borovicka, J., *et al.* (2015). Laparoscopic mesh-augmented hiatoplasty with cardiophrenicopexy versus laparoscopic Nissen fundoplication for the treatment of gastroesophageal reflux disease: a double-center randomized controlled trial. Ann Surg *262*, 721–725.

Naylor, C.D. (1997). Meta-analysis and the meta-epidemiology of clinical research. BMJ *315*, 617-619.

Neugebauer, E., Troidl, H., Kum, C.K., Eypasch, E., Miserez, M., and Paul, A. (1995). The E.A.E.S. Consensus Development Conferences on laparoscopic cholecystectomy, appendectomy, and hernia repair. Consensus statements--September 1994. The Educational Committee of the European Association for Endoscopic Surgery. Surg Endosc *9*, 550-563.

Neugebauer, E., Troidl, H., Spangenberger, W., Dietrich, A., and Lefering, R. (1991). Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. Cholecystectomy Study Group. Br J Surg *78*, 150-154.

Nijjar, R.S., Watson, D.I., Jamieson, G.G., Archer, S., Bessell, J.R., Booth, M., Cade, R., Cullingford, G.L., Devitt, P.G., Fletcher, D.R., *et al.* (2010). Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg *145*, 552–557.

Nissen, R. (1956). [A simple operation for control of reflux oesophagitis]. Schweiz Med Wschr *86*, 590–592.

Noblett, S.E., Watson, D.S., Huong, H., Davison, B., Hainsworth, P.J., and Horgan, A.F. (2006). Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. Colorectal Dis *8*, 563-569.

Nygren, J. (2006). The metabolic effects of fasting and surgery. Best Pract Res Clin Anaesthesiol *20*, 429-438.

Nygren, J., Soop, M., Thorell, A., Efendic, S., Nair, K.S., and Ljungqvist, O. (1998). Preoperative oral carbohydrate administration reduces postoperative insulin resistance. Clinical Nutrition *17*, 65-71.

Nygren, J., Thacker, J., Carli, F., Fearon, K.C., Norderval, S., Lobo, D.N., Ljungqvist, O., Soop, M., Ramirez, J., Enhanced Recovery After Surgery Society, f.P.C., *et al.* (2013). Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg *37*, 285-305.

O'Boyle, C.J., Watson, D.I., Jamieson, G.G., Myers, J.C., Game, P.A., and Devitt, P.G. (2002). Division of short gastric vessels at laparoscopic Nissen fundoplication: a prospective double-blind randomized trial with 5-year follow-up. Ann Surg *235*, 165–170.

Odgaard-Jensen, J., Vist, G.E., Timmer, A., Kunz, R., Akl, E.A., Schunemann, H., Briel, M., Nordmann, A.J., Pregno, S., and Oxman, A.D. (2011). Randomisation to protect against selection bias in healthcare trials. Cochrane Database Syst Rev, MR000012.

Oxman, A.D., and Guyatt, G.H. (1993). The science of reviewing research. Ann N Y Acad Sci *703*, 125-133; discussion 133-124.

Ozdemir, F., Eti, Z., Dincer, P., Gogus, F.Y., and Bekiroglu, N. (2011). [The Effect of Preoperative Oral Carbohydrate Loading on Stress Response in Patients Undergoing Major or Minor Surgery]. Turk Klin Tip Bilim *31*, 1392-1400.

Padwal, R., Klarenbach, S., Wiebe, N., Birch, D., Karmali, S., Manns, B., Hazel, M., Sharma, A.M., and Tonelli, M. (2011). Bariatric surgery: a systematic review and network meta-analysis of randomized trials. Obes Rev *12*, 602-621.

Palmer, S.C., Mavridis, D., Navarese, E., Craig, J.C., Tonelli, M., Salanti, G., Wiebe, N., Ruospo, M., Wheeler, D.C., and Strippoli, G.F. (2015). Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet *385*, 2047-2056.

Patel, S.V., Patel, S.V., Ramagopalan, S.V., and Ott, M.C. (2013). Laparoscopic surgery for Crohn's disease: a meta-analysis of perioperative complications and long term outcomes compared with open surgery. BMC Surg *13*, 14.

Patterson, E.J., Herron, D.M., Hansen, P.D., Ramzi, N., Standage, B.A., and Swanstrom, L.L. (2000). Effect of an esophageal bougie on the incidence of dysphagia following Nissen fundoplication - a prospective, blinded, randomized clinical trial. Arch Surg *135*, 1055–1061.

Penninga, L., Gluud, C., and Wetterslev, J. (2014). Meta-analysis of randomised trials on laparoscopic versus open surgery for acute appendicitis: has firm evidence been reached? J Gastrointest Surg *18*, 1383-1384.

Perrone, F., da-Silva, A.C., Adomo, I.F., Anabuki, N.T., Leal, F.S., Colombo, T., da Silva, B.D., Dock-Nascimento, D.B., Damiao, A., and de Aguilar-Nascimento, J.E. (2011). Effects of preoperative feeding with a whey protein plus carbohydrate drink on the acute phase response and insulin resistance. A randomized trial. Nutrition J *10*.

Peters, M.J., Mukhtar, A., Yunus, R.M., Khan, S., Pappalardo, J., Memon, B., and Memon, M.A. (2009). Meta-analysis of randomized clinical trials comparing open and laparoscopic anti-reflux surgery. American J Gastroenterol *104*, 1548-1562.

Pexe-Machado, P.A., de Oliveira, B.D., Dock-Nascimento, D.B., and de Aguilar-Nascimento, J.E. (2013). Shrinking preoperative fast time with maltodextrin and protein hydrolysate in gastrointestinal resections due to cancer. Nutrition *29*, 1054-1059.

Pham, C.T., Perera, C.L., Watkin, D.S., and Maddern, G.J. (2009). Laparoscopic ventral hernia repair: a systematic review. Surg Endosc *23*, 4-15.

Potter, S., Mills, N., Cawthorn, S.J., Donovan, J., and Blazeby, J.M. (2014). Time to be BRAVE: is educating surgeons the key to unlocking the potential of randomised clinical trials in surgery? A qualitative study. Trials *15*, 80.

Pronin, E., Lin, D.Y., and Ross, L. (2002). The bias blind spot: perceptions of bias in self versus others. Personality Social Psychol Bull *28*, 369-381.

Qin, M., Ding, G., and Yang, H. (2013). A clinical comparison of laparoscopic Nissen and Toupet fundoplication for gastroesophageal reflux disease. J Laparoendosc Adv A *23*, 601–604.

RACS (2019). Critical Literature Evaluation and Research (CLEAR). https://www.surgeons.org/for-health-professionals/register-courses-events/skills-training-courses/clear/ Accessed April 08, 2019

Raksakietisak, M., Chinachoti, T., Iamaroon, A., Thabpenthai, Y., Halilamien, P., Siriratwarangkul, S., and Watanitanon, A. (2014). Oral rehydration with 10% carbohydrate drink for preventing postoperative nausea and vomiting (PONV) after low dose of spinal morphine. J Med Assoc Thailand (Chotmaihet Thangphaet) *97*, 530-535.

Rapp-Kesek, D., Stridsberg, M., Andersson, L.G., Berne, C., and Karlsson, T. (2007). Insulin resistance after cardiopulmonary bypass in the elderly patient. Scand Cardiovasc J *41*, 102-108.

Raue, W., Ordemann, J., Jacobi, C.A., Menenakos, C., Buchholz, A., and Hartmann, J. (2011). Nissen versus Dor fundoplication for treatment of gastroesophageal reflux disease: a blinded randomized clinical trial. Digest Surg *28*, 80–86.

Reoch, J., Mottillo, S., Shimony, A., Filion, K.B., Christou, N.V., Joseph, L., Poirier, P., and Eisenberg, M.J. (2011). Safety of laparoscopic vs open bariatric surgery: a systematic review and meta-analysis. Arch Surg *146*, 1314-1322.

Reynolds, L.A., and Tansey, E.M. (2005). Prenatal corticosteroids for reducing morbidity and mortality after preterm birth, Vol 25 (London: The Wellcome Trust Centre for the History of Medicine at UCL).

Riley, R.D., Jackson, D., Salanti, G., Burke, D.L., Price, M., Kirkham, J., and White, I.R. (2017). Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. BMJ *358*, j3932.

Roks, D.J., Broeders, J.A., and Baigrie, R.J. (2017). Long-term symptom control of gastro-oesophageal reflux disease 12 years after laparoscopic Nissen or 180 degrees anterior partial fundoplication in a randomized clinical trial. Brit J Surg *104*, 852–856.

Roks, D.J., Koetje, J.H., Oor, J.E., Broeders, J.A., Nieuwenhuijs, V.B., and Hazebroek, E.J. (2017). Randomized clinical trial of 270 degrees posterior versus 180 degrees anterior partial laparoscopic fundoplication for gastro-oesophageal reflux disease. Brit J Surg *104*, 843–851.

Rothenberger, D.A. (2004). Evidence-based practice requires evidence. Br J Surg *91*, 1387-1388.

Russell, I. (1995). Evaluating new surgical procedures. BMJ *311*, 1243-1244.

Rydberg, L., Ruth, M., Abrahamsson, H., and Lundell, L. (1999). Tailoring antireflux surgery: a randomized clinical trial. World J Surg *23*, 612–618.

Sackett, D.L. (2007). Commentary: Measuring the success of blinding in RCTs: don't, must, can't or needn't? Int J Epidemiol *36*, 664-665.

Sackett, D.L., Rosenberg, W.M., Gray, J.A., Haynes, R.B., and Richardson, W.S. (1996). Evidence based medicine: what it is and what it isn't. BMJ *312*, 71-72.

Sada, F., Krasniqi, A., Hamza, A., Gecaj-Gashi, A., Bicaj, B., and Kavaja, F. (2014). A randomized trial of preoperative oral carbohydrates in abdominal surgery. BMC anesthesiology *14*, 93.

Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Syn Meth *3*, 80–97.

Salanti, G., Del Giovane, C., Chaimani, A., Caldwell, D.M., and Higgins, J.P. (2014). Evaluating the quality of evidence from a network meta-analysis. PLoS One *9*, e99682.

Salanti, G., Higgins, J.P., Ades, A.E., and Ioannidis, J.P. (2008). Evaluation of networks of randomized trials. Stat Methods Med Res *17*, 279-301.

Salanti, G., Kavvoura, F.K., and Ioannidis, J.P. (2008). Exploring the geometry of treatment networks. Ann Intern Med *148*, 544-553.

Sammour, T., Kahokehr, A., Srinivasa, S., Bissett, I.P., and Hill, A.G. (2011). Laparoscopic colorectal surgery is associated with a higher intraoperative complication rate than open surgery. Ann Surg *253*, 35-43.

Sauerland, S., Jaschinski, T., and Neugebauer, E.A. (2010). Laparoscopic versus open surgery for suspected appendicitis. Cochrane Database Syst Rev, CD001546.

Sauerland, S., Lefering, R., and Neugebauer, E.A. (1999). The pros and cons of evidence-based surgery. Langenbecks Arch Surg *384*, 423-431.

Savovic, J., Jones, H.E., Altman, D.G., Harris, R.J., Juni, P., Pildal, J., Als-Nielsen, B., Balk, E.M., Gluud, C., Gluud, L.L., *et al.* (2012). Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med *157*, 429-438.

Schollmeyer, T., Soyinka, A.S., Schollmeyer, M., and Meinhold-Heerlein, I. (2007). Georg Kelling (1866-1945): the root of modern day minimal invasive surgery. A forgotten legend? Arch Gynecol Obstet *276*, 505-509.

Schulz, K.F., Altman, D.G., Moher, D., and Group, C. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ *340*, c332.

Schulz, K.F., Chalmers, I., Hayes, R.J., and Altman, D.G. (1995). Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA *273*, 408-412.

Schulz, K.F., and Grimes, D.A. (2002). Blinding in randomised trials: hiding who got what. Lancet *359*, 696-700.

Schwarzer, G. (2016). meta: General package for meta-analysis. R package version 4.4-1. https://CRAN.R-project.org/package=meta Accessed July 28, 2016

Segol, P., Hay, J.M., and Pottier, D. (1989). [Surgical treatment of gastroesophageal reflux - Nissen fundoplication, Toupet posterior fundoplication or Lortat-Jacob cardiophrenopexy - a multicenter randomized trial]. Gastroen Clin Biol *13*, 873–879.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., and Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ *350*, g7647.

Shan, C.X., Zhang, W., Zheng, X.M., Jiang, D.Z., Liu, S., and Qiu, M. (2010). Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. World J Gastroenterol *16*, 3063–3071.

Sharp, S. (1998). sbe23: Meta-analysis regression. Stata Tech Bull *42*, 16-22.

Shaw, J.M., Bornman, P.C., Callanan, M.D., Beckingham, I.J., and Metz, D.C. (2010). Long-term outcome of laparoscopic Nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: a prospective, randomized trial. Surg Endosc *24*, 924–932.

Shun-Shin, M.J., and Francis, D.P. (2013). Why even more clinical research studies may be false: effect of asymmetrical handling of clinically unexpected values. PLoS One *8*, e65323.

Shun-Shin, M.J., Howard, J.P., and Francis, D.P. (2014). Removing the hype from hypertension. BMJ *348*, g1937.

Siersma, V., Als-Nielsen, B., Chen, W., Hilden, J., Gluud, L.L., and Gluud, C. (2007). Multivariable modelling for meta-epidemiological assessment of the association between trial quality and treatment effects estimated in randomized clinical trials. Stat Med *26*, 2745-2758.

Sihvonen, R., Paavola, M., Malmivaara, A., Itala, A., Joukainen, A., Nurmi, H., Kalske, J., Jarvinen, T.L., and Finnish Degenerative Meniscal Lesion Study, G. (2013). Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N Engl J Med *369*, 2515-2524.

Simillis, C., Thoukididou, S.N., Slesser, A.A., Rasheed, S., Tan, E., and Tekkis, P.P. (2015). Systematic review and network meta-analysis comparing clinical outcomes and effectiveness of surgical treatments for haemorrhoids. Br J Surg *102*, 1603-1618.

Sinclair, J.C. (1995). Meta-analysis of randomized controlled trials of antenatal corticosteroid for the prevention of respiratory distress syndrome: discussion. Am J Obstet Gynecol *173*, 335-344.

Singh, B.N., Dahiya, D., Bagaria, D., Saini, V., Kaman, L., Kaje, V., Vagadiya, A., Sarin, S., Edwards, R., Attri, V., *et al.* (2015). Effects of preoperative carbohydrates drinks on immediate postoperative outcome after day care laparoscopic cholecystectomy. Surg Endosc *29*, 3267-3272.

Siontis, G.C., Stefanini, G.G., Mavridis, D., Siontis, K.C., Alfonso, F., Perez-Vizcayno, M.J., Byrne, R.A., Kastrati, A., Meier, B., Salanti, G., *et al.* (2015). Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet *386*, 655-664.

Slim, K., Panis, Y., Chipponi, J., and Societe Francaise de Chirurgie, D. (2004). Half of the currecnt practice of gastrointestinal surgery is against the evidence: a survery of the French Society of Digestive Surgery. J Gastrointest Surg *8*, 1079-1082.

Smith, I., Kranke, P., Murat, I., Smith, A., O'Sullivan, G., Soreide, E., Spies, C., in't Veld, B., and European Society of, A. (2011). Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol *28*, 556-569.

Smith, M.D., McCall, J., Plank, L., Herbison, G.P., Soop, M., and Nygren, J. (2014). Preoperative carbohydrate treatment for enhancing recovery after elective surgery. Cochrane Database of Systematic Reviews *8*, CD009161.

Solomon, M.J., and McLeod, R.S. (1995). Should we be performing more randomized controlled trials evaluating surgical operations? Surgery *118*, 459-467.

Solomon, M.J., Young, C.J., Eyers, A.A., and Roberts, R.A. (2002). Randomized clinical trial of laparoscopic versus open abdominal rectopexy for rectal prolapse. Br J Surg *89*, 35-39.

Sonawalla, S.B., and Rosenbaum, J.F. (2002). Placebo response in depression. Dialogues Clin Neurosci *4*, 105-113.

Song, F., Loke, Y.K., Walsh, T., Glenny, A.M., Eastwood, A.J., and Altman, D.G. (2009). Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ *338*, b1147.

Soop, M., Nygren, J., Myrenfors, P., Thorell, A., and Ljungqvist, O. (2001). Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. Am J Physiol Endocrinol Metab *280*, E576-583.

Soop, M., Nygren, J., Thorell, A., Weidenhielm, L., Lundberg, M., Hammarqvist, F., and Ljungqvist, O. (2004). Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. Clinical Nutrition *23*, 733-741.

Spanos, N.P., Burgess, C.A., Cross, P.A., and MacLeod, G. (1992). Hypnosis, reporting bias, and suggested negative hallucinations. J Abnorm Psychol *101*, 192-199.

Spence, G.M., Watson, D.I., Jamiesion, G.G., Lally, C.J., and Devitt, P.G. (2006). Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg *10*, 698–705.

Stefanidis, D., Hope, W.W., Kohn, G.P., Reardon, P.R., Richardson, W.S., Fanelli, R.D., and Comm, S.G. (2010). Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc *24*, 2647–2669.
Sterne, J.A., Juni, P., Schulz, K.F., Altman, D.G., Bartlett, C., and Egger, M. (2002). Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med *21*, 1513-1524.

Stirrat, G.M., Farrow, S.C., Farndon, J., and Dwyer, N. (1992). The challenge of evaluating surgical procedures. Ann R Coll Surg Engl *74*, 80-84.

Strate, U., Emmermann, A., Fibbe, C., Layer, P., and Zornig, C. (2008). Laparoscopic fundoplication: Nissen versus Toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility. Surg Endosc *22*, 21–30.

Stuart, R.C., Dawson, K., Keeling, P., Byrne, P.J., and Hennessy, T.P. (1989). A prospective randomized trial of Angelchik prosthesis versus Nissen fundoplication. Brit J Surg *76*, 86–89.

Sun, X., Ioannidis, J.P., Agoritsas, T., Alba, A.C., and Guyatt, G. (2014). How to use a subgroup analysis: users' guide to the medical literature. JAMA *311*, 405-411.

Swan, P., Haydock, M., Amer, M., Bartlett, A., and McCall, J. (2017). A systematic review and multiple treatment meta-analysis of targeted therapies for the treatment of early hepatocellular carcinoma. In The 11th International Liver Cancer Association Annual Conference (Seoul, South Korea).

Tan, G., Yang, Z., and Wang, Z. (2011). Meta-analysis of laparoscopic total (Nissen) versus posterior (Toupet) fundoplication for gastro-oesophageal reflux disease based on randomized clinical trials. ANZ J Surg *81*, 246–252.

Thompson, S.K., and Watson, D.I. (2015). What is the best anti-reflux operation? All fundoplications are not created equal. World J Surg *39*, 997–999.

Thor, K.B., and Silander, T. (1989). A long-term randomized prospective trial of the Nissen procedure versus a modified Toupet technique. Ann Surg *210*, 719–724.

Tou, S., Brown, S.R., Malik, A.I., and Nelson, R.L. (2008). Surgery for complete rectal prolapse in adults. Cochrane Database Syst Rev, CD001758.

Tran, S., Wolever, T.M., Errett, L.E., Ahn, H., Mazer, C.D., and Keith, M. (2013). Preoperative carbohydrate loading in patients undergoing coronary artery bypass or spinal surgery. Anesth Analg *117*, 305-313.

Varin, O., Velstra, B., De Sutter, S., and Ceelen, W. (2009). Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg *144*, 273–278.

Vecht, J.A., Athanasiou, T., Ashrafian, H., Mayer, E., Darzi, A., and von Segesser, L.K. (2009). Surgeons produce innovative ideas which are frequently lost in the labyrinth of patents. Eur J Cardiothorac Surg *35*, 480-488.

Vennix, S., Pelzers, L., Bouvy, N., Beets, G.L., Pierie, J.P., Wiggers, T., and Breukink, S. (2014). Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev, CD005200.

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. J Stat Soft *36*, 1-48.

Vinuela, E.F., Gonen, M., Brennan, M.F., Coit, D.G., and Strong, V.E. (2012). Laparoscopic versus open distal gastrectomy for gastric cancer: a meta-analysis of randomized controlled trials and high-quality nonrandomized studies. Ann Surg *255*, 446-456.

Walker, S.J., Holt, S., Sanderson, C.J., and Stoddard, C.J. (1992). Comparison of Nissen total and Lind partial transabdominal fundoplication in the treatment of gastro-oesophageal reflux. Brit J Surg *79*, 410–414.

Wang, B., Zhang, W., Liu, S., Du, Z., Shan, C., and Qiu, M. (2015). A Chinese randomized prospective trial of floppy Nissen and Toupet fundoplication for gastroesophageal disease. Int J Surg *23*, 35–40.

Wang, Z.G., Wang, Q., Wang, W.J., and Qin, H.L. (2010). Randomized clinical trial to compare the effects of preoperative oral carbohydrate versus placebo on insulin resistance after colorectal surgery. Brit J Surg *97*, 317-327.

Wartolowska, K., Judge, A., Hopewell, S., Collins, G.S., Dean, B.J., Rombach, I., Brindley, D., Savulescu, J., Beard, D.J., and Carr, A.J. (2014). Use of placebo controls in the evaluation of surgery: systematic review. BMJ *348*, g3253.

Washer, G.F., Gear, M.W., Dowling, B.L., Gillison, E.W., Royston, C.M., and Spencer, J. (1984). Randomized prospective trial of Roux-en-Y duodenal diversion versus fundoplication for severe reflux oesophagitis. Brit J Surg *71*, 181–184.

Watson, D.I., Devitt, P.G., Smith, L., and Jamieson, G.G. (2012). Anterior 90 degrees partial vs Nissen fundoplication - 5 Year follow-up of a single-centre randomised trial. J Gastrointest Surg *16*, 1653–1658.

Watson, D.I., Jamieson, G.G., Lally, C., Archer, S., Bessell, J.R., Booth, M., Cade, R., Cullingford, G., Devitt, P.G., Fletcher, D.R., *et al.* (2004). Multicenter, prospective, double-blind, randomized trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg *139*, 1160–1167.

Watson, D.I., Jamieson, G.G., Pike, G.K., Davies, N., Richardson, M., and Devitt, P.G. (1999). Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Brit J Surg *86*, 123–130.

Watson, D.I., Pike, G.K., Baigrie, R.J., Mathew, G., Devitt, P.G., Britten-Jones, R., and Jamieson, G.G. (1997). Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. Ann Surg *226*, 642–652.

Waxman, B.P. (2016). Medicine in small doses. ANZ J Surg *86*, 541.

White, I.R. (2009). Multivariate random-effects meta-analysis. Stata J *9*, 40-56.

White, I.R. (2011). Multivariate random-effects meta-regression: Updates to mvmeta. Stata J *11*, 255-270.

White, I.R. (2015). Network meta-analysis. Stata J *15*, 951-985.

White, I.R., Barrett, J.K., Jackson, D., and Higgins, J.P. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Syn Meth *3*, 111-125.

Wileman, S.M., McCann, S., Grant, A.M., Krukowski, Z.H., and Bruce, J. (2010). Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev *3*, CD003243.

Wilson, C.H., Sanni, A., Rix, D.A., and Soomro, N.A. (2011). Laparoscopic versus open nephrectomy for live kidney donors. Cochrane Database Syst Rev, CD006124.

Wood, L., Egger, M., Gluud, L.L., Schulz, K.F., Juni, P., Altman, D.G., Gluud, C., Martin, R.M., Wood, A.J., and Sterne, J.A. (2008). Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ *336*, 601-605.

Woodcock, S.A., Watson, D.I., Lally, C., Archer, S., Bessell, J.R., Booth, M., Cade, R., Cullingford, G.L., Devitt, P.G., Fletcher, D.R., *et al.* (2006). Quality of life following laparoscopic anterior 90 degrees versus Nissen fundoplication: results from a multicenter randomized trial. World J Surg *30*, 1856–1863.

Woodfield, J., Schmidt, B., Amer, M., and McCall, J. (2017). Network meta-analysis of bowel preparation in elective colorectal surgery. PROSPERO CRD42017059746. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017059746

Wu, S., Cipriani, A., Yang, Z., Yang, J., Cai, T., Xu, Y., Quan, X., Zhang, Y., Chai, S., Sun, F., *et al.* (2018). The cardiovascular effect of incretin-based therapies among type 2 diabetes: a systematic review and network meta-analysis. Expert Opin Drug Saf *17*, 243-249.

Yang, H., Watson, D.I., Lally, C.J., Devitt, P.G., Game, P.A., and Jamieson, G.G. (2008). Randomized trial of division versus nondivision of the short gastric vessels during laparoscopic Nissen fundoplication: 10-year outcomes. Ann Surg *247*, 38–42.

Yang, Y., Yan-Bing, Z., Xue-Long, J., Dong, C., and Zhi-Hao, W. (2012). Effects and safety of preoperative oral carbohydrate in radical distal gastrectomy - a randomized clinical trial. J Cancer Sci Ther *4*, 116-119.

Yigit, T., Coskun, A.K., Sinan, H., Harlak, A., Kantarcioglu, M., Kilbas, Z., Kozak, O., and Cetiner, S. (2012). Rectus abdominus fascial sheath usage for crural reinforcement during surgical management of GERD: preliminary report of a prospective randomized clinical trial. Surg Laparosc Endosc Per *22*, 333–337.

Yildiz, H., Gunal, S.E., Yilmaz, G., and Yucel, S. (2013). Oral carbohydrate supplementation reduces preoperative discomfort in laparoscopic cholecystectomy. J Invest Surg *26*, 89-95.

Yilmaz, N., Cekmen, N., Bilgin, F., Erten, E., Ozhan, M.O., and Cosar, A. (2013). Preoperative carbohydrate nutrition reduces postoperative nausea and vomiting compared to preoperative fasting. J Res Med Sci *18*, 827-832.

Yuill, K.A., Richardson, R.A., Davidson, H.I., Garden, O.J., and Parks, R.W. (2005). The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. Clinical Nutrition *24*, 32-37.

Zargar-Shoshtari, K., and Hill, A.G. (2008). Optimization of perioperative care for colonic surgery: a review of the evidence. ANZ J Surg *78*, 13-23.

Zelic, M., Stimac, D., Mendrila, D., Tokmadzic, V.S., Fisic, E., Uravic, M., and Sustic, A. (2012). Influence of preoperative oral feeding on stress response after resection for colon cancer. Hepato-Gastroenterol *59*, 1385-1389.

Zornig, C., Strate, U., Fibbe, C., Emmermann, A., and Layer, P. (2002). Nissen vs Toupet laparoscopic fundoplication. Surg Endosc *16*, 758–766.

APPENDIX A

Published papers

A1 Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery

Systematic review

Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery

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Background: Three meta-analyses have summarized the effects of preoperative carbohydrate administration on postoperative outcomes in adult patients undergoing elective surgery. However, these studies could not account for the different doses of carbohydrate administered and the different controls used. Multiple-treatments meta-analysis allows robust synthesis of all available evidence in these situations.

Methods: Article databases were searched systematically for RCTs comparing preoperative carbohydrate administration with water, a placebo drink, or fasting. A four-treatment multiple-treatments meta-analysis was performed comparing two carbohydrate dose groups (low, 10–44 g; high, 45 g or more) with two control groups (fasting; water or placebo). Primary outcomes were length of hospital stay and postoperative complication rate. Secondary outcomes included postoperative insulin resistance, vomiting and fatigue.

Results: Some 43 trials involving 3110 participants were included. Compared with fasting, preoperative low-dose and high-dose carbohydrate administration decreased postoperative length of stay by 0·4 (95 per cent c.i. 0·03 to 0·7) and 0·2 (0·04 to 0·4) days respectively. There was no significant decrease in length of stay compared with water or placebo. There was no statistically significant difference in the postoperative complication rate, or in most of the secondary outcomes, between carbohydrate and control groups.

Conclusion: Carbohydrate loading before elective surgery conferred a small reduction in length of postoperative hospital stay compared with fasting, and no benefit in comparison with water or placebo.

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Introduction

Enhanced recovery after surgery (ERAS), or fast-track recovery, is a set of perioperative principles and strategies brought together in an integrated pathway to optimize patients' operative journeys and minimize morbidity. ERAS protocols are now in widespread use across many surgical disciplines internationally, as they have been shown to reduce complications, facilitate recovery and hasten discharge[1].

However, the evidence supporting the use of some individual components of ERAS is variable, so that their routine inclusion in ERAS protocols remains debatable[2]. An example is the preoperative administration of a carbohydrate load, usually as an oral solution, promoted as a counter to postoperative hyperglycaemia[3].

Surgery, as a form of stress, is known to induce peripheral insulin resistance, which can lead to hyperglycaemia, which, in turn, may lead to postoperative complications and prolonged recovery[4]. Studies have shown that a preoperative carbohydrate load large enough to stimulate a prompt insulin response decreases postoperative insulin resistance by approximately 50 per cent[3]. More than 30 RCTs have investigated whether this effect results in improved postoperative outcomes. These RCTs have recently been summarized in several meta-analyses[5,6], including a Cochrane review[7].

However, these meta-analyses resulted in variable conclusions, due partly to the use of different inclusion and exclusion criteria, so that different RCTs were included in each meta-analysis. More importantly, however, a standard pairwise meta-analysis cannot account for the different carbohydrate doses and controls used in the included RCTs. As a result, these meta-analyses either combined different control groups (such as fasting, water and placebo) into one treatment arm[5,7] or performed several different head-to-head meta-analyses[6,7], thereby limiting their interpretability. Thus, there remains a need for an inclusive, methodologically sound, analysis of all the available evidence, to resolve ongoing uncertainty around the true clinical value of carbohydrate loading[8].

Multiple-treatments meta-analysis offers a validated method of synthesis in instances such as this, where multiple intervention or control treatments have been compared for the same condition in head-to-head RCTs[9]. This type of meta-analysis employs the large amount of indirect evidence available in addition to the direct evidence, thus increasing the precision of the effect estimate[10,11]. Moreover, multiple-treatments meta-analysis enables visualization of all the available evidence, and a ranking of all the treatments available. This study employed multiple-treatments meta-analysis to determine the effects of preoperative carbohydrate administration on clinically relevant postoperative outcomes in adult patients undergoing elective surgery.

Methods

Search strategy and selection criteria

A systematic review of RCTs of preoperative carbohydrate administration for elective surgical patients was performed, using the process detailed in the Cochrane review[7]. In brief, article databases and trial registries were searched to June 2016, using a structured sensitivity-maximizing search strategy and no language restrictions. Two authors independently screened all titles and abstracts for eligibility, and trial authors were contacted when further information was required to determine eligibility.

All randomized and quasi-randomized trials comparing the preoperative administration of at least 10 g carbohydrate (orally or intravenously) within 4 h of surgery start time, with fasting, water or placebo, to adults undergoing any type of elective surgical procedure, were included. Studies that co-administered other substances (such as glutamine) were included, as long as the dose of carbohydrate was 10 g or more. Studies that administered carbohydrate more than 4 h before surgery, and those that included patients undergoing emergency surgery (defined as within 24 h of first physician contact), were excluded.

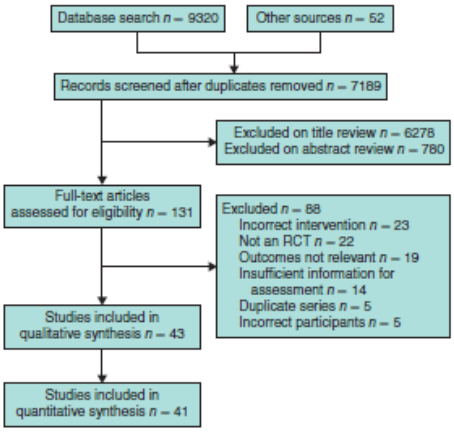

Fig. 1 PRISMA flow chart for the study

Outcome measures

All trials that reported the primary outcomes including length of postoperative stay (in days) or postoperative complication rate (as defined by trial authors) were selected. Trials that reported any of the following secondary outcomes were also included: aspiration pneumonitis rate (defined as observed regurgitation or vomiting in association with abnormal chest imaging); vomiting within the first 24 h after surgery (measured as an incidence count); insulin resistance (measured by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) method); insulin sensitivity (measured by the hyperinsulinaemic–euglycaemic clamp method); nausea at 24 h after surgery, postoperative general well-being and postoperative fatigue (all measured on ordinal, visual analogue or composite scales); and return of intestinal function (number of postoperative days to first passage of flatus, and first bowel motion).

Data extraction and quality assessment

For studies that were also included in the Cochrane review[7], data that had already been extracted were used. For the additional studies included in the present study, the same structured paper form used in the Cochrane review was employed to collect extracted data. Extracted

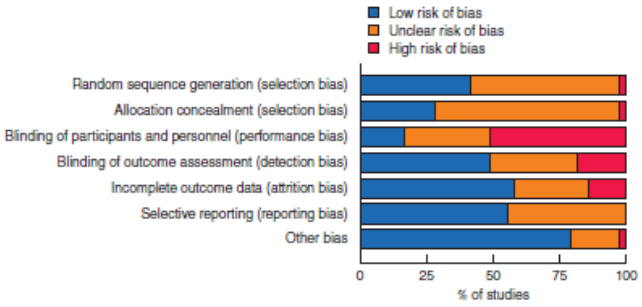

Fig. 2 Risk-of-bias summary figure

data included study characteristics, patient characteristics, intervention details and outcome measures. Study authors were contacted to request missing data necessary for multiple-treatments meta-analysis.

Missing standard deviations were calculated from standard errors or confidence intervals, as described in the Cochrane Handbook[12], or from ranges or interquartile ranges, as described by Hozo and colleagues[13]. When standard deviations could not be calculated, and attempts to contact the study authors were exhausted, they were imputed using the median of reported standard deviations from other similar trials.

The methodological quality of all included trials was assessed using the Cochrane risk-of-bias tool[12], across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was assessed as high, low or unclear risk.

Statistical analysis

A random-effects multiple-treatments meta-analysis was performed using the suite of Stata® (StataCorp, College Station, Texas, USA) routines developed specifically for this purpose[14–16]. The main analysis comprised four treatment groups (nodes): low-dose carbohydrate (10–44 g), high-dose carbohydrate (45 g or more), water or placebo, and fasting. Fasting was allocated as the reference treatment in the network. Comparisons between the water/placebo group and the fasting group are not reported, as this review does not include all RCTs that compared preoperative fasting with water only. A network map was produced to provide a visual summary of the network of evidence available.

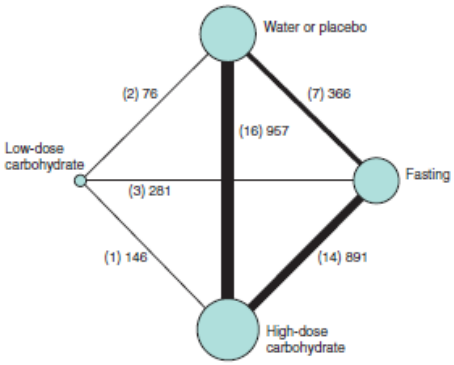

Fig. 3 Network map of evidence. The size of each circle (node) is proportional to the number of patients who received the treatment. The width of the lines represents the number of RCTs that directly compared the connected pair of treatments. The values in parentheses denote the number of RCTs that investigated the associated comparison, followed by the combined number of patients in those RCTs

The results for continuous data are summarized as the mean difference (MD – with units) or standardized mean difference (SMD – expressed as standard deviations), as appropriate, with 95 per cent confidence intervals. The SMD was used when studies assessing the same outcome used different measures, or the results for that outcome were substantially different owing to study population differences. Categorical data were summarized as odds ratios (ORs) with 95 per cent confidence intervals (see also *Appendix S1*, supporting information). When SMD was appropriate, the original result is reported in standard

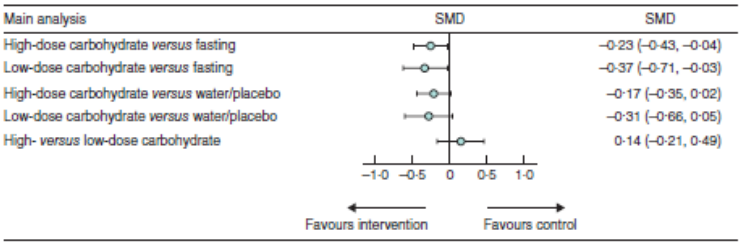

Fig. 4 Composite forest plot of comparisons for length of postoperative stay. Values are standardized mean differences (SMDs) (expressed as standard deviations) with 95 per cent confidence intervals

deviations, as well as the back-transformed approximations to the initial unit[12].

For primary outcomes with statistically significant differences between the groups, the probability of each treatment group ranking as the best, second, third or worst treatment in the network was calculated, and presented as a rankogram if one treatment was clearly superior (greater than 90 per cent probability of ranking best)[17]. A meta-regression analysis for those outcomes was also performed to evaluate further any relationship with carbohydrate dose. A cumulative meta-analysis for the outcome length of postoperative stay was also performed, as well as several subgroup and sensitivity analyses, including testing for heterogeneity and publication bias (*Appendix S1*, supporting information).

Results

Search results and study characteristics

Fig. 1 summarizes the database search and study selection process. Forty-three RCTs[18–60], involving 3110 patients, fulfilled the inclusion criteria. One trial[19] could not be included in the multiple-treatments meta-analysis as the only relevant reported outcome was the aspiration pneumonitis rate, which was zero across all groups in all RCTs. Another trial[51] reported nausea as a mean incidence rate, which could not be included in the multiple-treatments meta-analysis but is included in the qualitative synthesis.

Table S1 summarizes the characteristics of included studies. Patients in the included RCTs underwent a wide variety of open and laparoscopic surgical procedures for benign and malignant pathology, including colorectal and upper gastrointestinal, endocrine, orthopaedic, cardiothoracic and gynaecological surgery. The majority of RCTs involved the administration of high-dose carbohydrate before surgery (mostly 45–55 g). In two studies[36,41] carbohydrate was administered intravenously, and only one study[36] directly compared low- and high-dose carbohydrate.

The risk-of-bias assessment of the included trials is summarized in *Fig. 2* (see also *Fig. S1*, supporting information, which shows the domain assessment for individual trials). Of the 43 included trials, only six[21,38,42,52,53,59] were adequately blinded with a low risk of performance or detection bias. There was evidence of selection bias in the majority of studies. Only two trials[38,42] were judged as at low risk of bias across all domains.

Primary outcomes

Length of postoperative stay

Length of postoperative stay was the most commonly reported outcome, and was therefore used for the sensitivity analyses and funnel plot. *Fig. 3* summarizes the network of direct evidence available for this outcome. This was reported by 25 studies[18,20,22–24,27,29–31,36,38,39,42,44–48,50,52–54,56,57,59] involving 1888 participants. Mean length of postoperative stay in the included studies ranged from 1 to 17 days. The multiple-treatments meta-analysis results are presented in *Fig. 4* and *Table 1*. Compared with fasting, patients administered carbohydrate before surgery were discharged earlier (high-dose carbohydrate: SMD 0·2 (95 per cent c.i. 0·04 to 0·4) standard deviations earlier; low-dose carbohydrate SMD 0·4 (0·03 to 0·7) standard deviations earlier). On back-transformation into days, high-dose carbohydrate administration decreased length of stay in patients undergoing major surgery (mean length of stay 2 days or more) by 0·7 (95 per cent c.i. 0·1 to 1·4) days, and for patients undergoing minor surgery (mean length of stay less than 2 days) by 0·07 (0·01 to 0·1) days. Compared with water or placebo, no benefit was shown for either low- or high-dose carbohydrate with respect to time to hospital discharge.

Table 1 Multiple-treatments meta-analysis results

	Versus fasting	*Versus* water/placebo	*Versus* low-dose CHO
Length of postoperative stay			
Primary analysis*			
High-dose CHO	−0·2 (−0·4, −0·04)**	−0·2 (−0·4, 0·02)	0·1 (−0·2, 0·5)
Low-dose CHO	−0·4 (−0·7, −0·03)**	−0·3 (−0·7, 0·05)	
Back-transformation†			
Major surgery (days)‡			
High-dose CHO	−0·7 (−1·4, −0·1)**	−0·7 (−1·4, 0·07)	0·3 (−0·7, 1·7)
Low-dose CHO	−1·4 (−2·4, −0·1)**	−1·0 (−2·4, 0·2)	
Minor surgery (days)§			
High-dose CHO	−0·07 (−0·1, −0·01)**	−0·07 (−0·1, 0·01)	0·04 (−0·07, 0·2)
Low-dose CHO	−0·1 (−0·2, −0·01)**	−0·1 (−0·2, 0·02)	
Subgroup analysis¶			
Major abdominal surgery (days)			
High-dose CHO	−1·7 (−3·2, −0·1)**	−1·4 (−2·7, −0·1)**	0·2 (−3·1, 3·6)
Low-dose CHO	−1·9 (−5·2, 1·5)	−1·6 (−5·1, 1·9)	
Minor abdominal surgery (days)			
High-dose CHO	−0·09 (−0·4, 0·2)	0·0 (−0·05, 0·05)	−0·02 (−0·4, 0·4)
Low-dose CHO	−0·07 (−0·5, 0·4)	0·02 (−0·4, 0·4)	
Orthopaedic surgery (days)			
High-dose CHO	−0·7 (−2·3, 1·0)	−0·3 (−1·0, 0·4)	−0·7 (−3·2, 1·9)
Low-dose CHO	0·0 (−2·0, 2·0)	−0·3 (−2·2, 2·9)	
Cardiac surgery (days)			
High-dose CHO	−0·5 (−3·4, 2·3)	0·4 (−3·1, 3·9)	2·4 (−2·5, 7·2)
Low-dose CHO	−2·9 (−7·8, 2·0)	−2·0 (−5·4, 1·5)	
Postoperative complication rate#			
High-dose CHO	1·02 (0·52, 2·00)	0·82 (0·55, 1·22)	1·04 (0·42, 2·58)
Low-dose CHO	0·99 (0·42, 2·32)	0·79 (0·30, 2·11)	
Vomiting#			
High-dose CHO	1·45 (0·67, 3·16)	1·19 (0·60, 2·38)	1·40 (0·58, 3·36)
Low-dose CHO	1·04 (0·64, 1·68)	0·85 (0·34, 2·11)	
Insulin resistance¶			
High-dose CHO	−2·2 (−4·3, −0·09)**	−2·5 (−4·9, −0·2)**	−0·8 (−4·5, 2·9)
Low-dose CHO	−1·4 (−4·9, 2·1)	−1·8 (−5·2, 1·7)	
Insulin sensitivity (ml per kg per min)¶∧			
High-dose CHO	1·2 (−1·0, 3·4)	0·2 (−0·7, 1·0)	
Nausea*∧			
High-dose CHO	−0·6 (−1·4, 0·07)	−0·7 (−1·1, −0·2)**	
Postoperative well-being*			
High-dose CHO	0·1 (−0·2, 0·4)	−0·01 (−0·3, 0·2)	0·06 (−0·6, 0·7)
Low-dose CHO	0·06 (−0·6, 0·7)	−0·01 (−0·8, 0·6)	
Postoperative fatigue*∧			
High-dose CHO	−0·08 (−0·7, 0·5)	0·1 (−0·3, 0·5)	
Time to first bowel motion (days)¶∧			
High-dose CHO	−0·5 (−1·6, 0·6)	−0·8 (−2·0, 0·3)	

Values in parentheses are 95 per cent confidence intervals. *Standardized mean difference (SMD) (expressed as standard deviations). †The SMD was converted back to a mean difference in days, using standard deviations reported in the included trials. ‡The mean standard deviation (3·4 days) of all trials reporting major surgery (mean length of stay greater than 2 days) was used in this calculation; mean length of stay in this group was 8·1 days. §The mean standard deviation (0·4 days) of all trials reporting minor surgery (mean length of stay less than 2 days) was used in this calculation; mean length of stay in this group was 1·1 days. ¶Mean difference. #Odds ratio. ∧No low-dose carbohydrate (CHO) data available for this outcome. **$P < 0·050$ (Wald test)

No statistically significant difference was found between the two carbohydrate groups in the network. None of the treatments was clearly superior on calculation of ranking probabilities for this outcome. Meta-regression also demonstrated no relationship between carbohydrate dose and length of postoperative stay, with none of the heterogeneity in the model explained by the dose of carbohydrate administered ($R^2 = 0$)[61] (*Fig. 5*). Cumulative meta-analysis of high-dose carbohydrate *versus* control demonstrated that further studies are unlikely to change this effect estimate significantly (*Fig. S2*, supporting information).

Testing for inconsistency between the direct and indirect evidence for this analysis yielded low inconsistency factors for all evidence loops, ranging from 0·06 to 0·4. There were

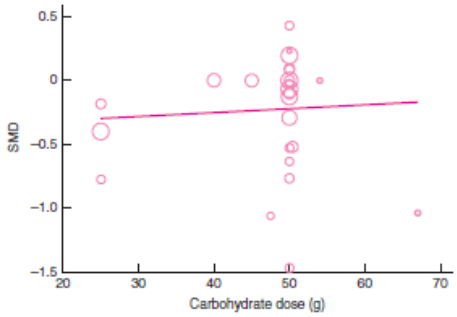

Fig. 5 Bubble plot (meta-regression) for length of postoperative stay. The circles represent the effect estimate for each study, sized according to the precision of each estimate. The line of best fit (regression line) is almost horizontal, suggesting no relationship between carbohydrate dose and length of postoperative stay

also no significant differences between the results obtained using the direct evidence alone, the indirect evidence alone, or the combined network. All predictive intervals for the comparisons in this analysis included zero, indicating moderate between-study heterogeneity. All sensitivity analyses showed results similar to those in the main analysis.

Results of subgroup analysis for this outcome are presented in *Table 1*. Except for two comparisons within the major abdominal surgery subgroup (defined as a mean length of postoperative stay of 2 days or more), none of the other subgroup comparisons showed a statistically significant difference. Inconsistency between the direct and indirect evidence for the major abdominal surgery subgroup was high (inconsistency factor of 2·4, with 95 per cent c.i. of up to 11·0), and all the predictive intervals in this subgroup included zero.

Visual inspection of a comparison-adjusted funnel plot for this outcome (*Fig. S3*, supporting information) suggests the presence of publication bias towards studies reporting a significant difference between the carbohydrate groups and controls.

Postoperative complication rate

This outcome was reported by 17 studies[22,27,28,31,36,38,42,44,46,47,52–54,56,58–60], involving 1094 participants. No multiple-treatments meta-analysis comparison for this outcome showed any statistically significant difference (*Table 1*). Sensitivity analysis showed that exclusion of one trial[54] with a much higher complication event rate than the others did not significantly alter the results. Inconsistency analysis showed no evidence of a significant difference between the direct and indirect evidence for this outcome (inconsistency factors ranging from 0·3 to 0·96).

Secondary outcomes

Aspiration pneumonitis

No aspiration pneumonitis events were reported in any of the 19 studies[19,21,24,27,33,34,38,42–44,46,48,52–57,59] that included this outcome. Therefore, a multiple-treatments meta-analysis was not performed.

Vomiting

Eight studies[21,28,29,31,33,34,48,56] reported the rate of postoperative vomiting, involving 840 participants. The multiple-treatments meta-analysis results are summarized in *Table 1*. There was no statistically significant difference between the groups in the network. Inconsistency for this analysis was low (inconsistency factor of up to 0·4).

Insulin resistance

Thirteen studies[24–29,42,46,47,49,54–56] were included, with data available for 503 participants. High-dose carbohydrate administration resulted in a statistically significant decrease in insulin resistance compared with fasting, and water or placebo, but with wide confidence intervals approaching non-significance (*Table 1*). One study[55] reported very different numerical results compared with the other trials, despite using the same methodology and formulas. Sensitivity analysis excluding this study showed no statistically significant differences between any of the groups. Inconsistency in this network was high (inconsistency factors of 2·4 and 4·8).

Insulin sensitivity

Four studies[40,41,52,53] measured insulin sensitivity using the hyperinsulinaemic–euglycaemic clamp method, with data available for 62 participants. No low-dose carbohydrate studies were available for this outcome. Multiple-treatments meta-analysis showed no significant difference in any of the comparisons (*Table 1*).

Other secondary outcomes

The results of the remaining secondary outcomes are shown in *Table 1* and *Appendix S2* (supporting information).

Discussion

This multiple-treatments meta-analysis shows that administration of a preoperative carbohydrate load, within 4 h of surgery start time, led to a small reduction in length of

postoperative stay in comparison with fasting, but no significant effect in comparison with allowing patients water, or a placebo drink, before surgery. Heterogeneity analysis for this outcome using predictive interval calculations showed moderate between-study heterogeneity, and evidence of publication bias was suggested on examination of the comparison-adjusted funnel plot. Further, sensitivity analysis, separating the water/placebo group into water and placebo, then the placebo subgroup into blinded and unblinded studies, showed no significant difference between any of the placebo and carbohydrate groups. In addition, a cumulative meta-analysis of this outcome suggests that future studies are unlikely to show a larger effect than that observed in this study.

SMD was used for length of postoperative stay to account for the wide variety in expected length of stay between the different procedures. Procedures with differing expected lengths of stay cannot be compared directly using the mean difference, as any effect of carbohydrate administration would be expected to be proportional to the actual length of stay. SMD can be interpreted using rules of thumb[12], where an SMD of 0·4 standard deviations or less is considered to indicate a small effect, suggesting that the difference between the carbohydrate and fasting groups was small. The back-transformation results support this conclusion, showing a reduction in length of stay of approximately 10 per cent in both carbohydrate groups compared with fasting, and no difference compared with water or placebo. It is important not to conclude from the subgroup analysis that the effect of preoperative carbohydrate loading on major abdominal surgery is larger than on other procedures, as the relative reduction in length of stay was similar between subgroups[62].

This multiple-treatments meta-analysis found no evidence that high-dose carbohydrate was more or less effective in reducing length of stay compared with low-dose carbohydrate. There were fewer data available for low-dose carbohydrate in the network, highlighted by wider confidence intervals than for the high-dose comparisons. Sensitivity analysis using meta-regression supported this finding, showing no evidence of a carbohydrate dose–response relationship.

There was no significant difference in the postoperative complication rate for patients given a carbohydrate load, compared with patients who remained fasted, or those given water or a placebo drink. Although high-dose carbohydrate conferred a reduction in nausea scores at 24 h compared with water or placebo, this was based on a small number of studies, and there was no statistically significant difference in the incidence of vomiting between the groups. No other significant differences were found between the carbohydrate and control groups in any of the other clinical secondary outcomes investigated. The confidence intervals for some of these outcomes were wide, however, reflecting a relative paucity of available data, and heterogeneity.

The effect of carbohydrate loading on postoperative insulin resistance was investigated, as it is this effect in particular that provided the rationale for introducing preoperative carbohydrate loading[3,63]. There was no statistically significant difference in insulin sensitivity in this multiple-treatments meta-analysis. This may, however, be a type II error (false-negative finding), as only four studies were available to assess insulin sensitivity. Further, a statistically significant difference was found in insulin resistance (measured by homeostatic modelling) between high-dose carbohydrate and both control treatment groups, although with high inconsistency and sensitivity analysis suggesting this finding was influenced by the reported results of a single study. A reduction in postoperative insulin resistance *per se* may not be clinically important unless it in turn leads to improved postoperative outcomes.

Three previous meta-analyses[5–7] have investigated the effect of preoperative carbohydrate loading. The findings of the present review are broadly consistent with the largest and most recent of these[7], which included 27 trials and found a small decrease (0·4 days) in length of postoperative stay for patients given a carbohydrate load (high dose) only in comparison with fasting, an increase in insulin sensitivity compared with the control treatments, and a shorter time to passage of flatus by less than half a day. No other significant differences were found for an identical set of outcomes as in the present review.

The use of multiple-treatments meta-analysis methodology in this study has allowed more data to be incorporated than in all previous reviews, as well as the use of all direct and indirect evidence available, thereby increasing the precision of the effect estimates. The fasting, water/placebo and carbohydrate dosing regimens were also analysed simultaneously as separate groups, in a manner that fully respects randomization[10] (unlike subgroup analysis[62]), thus eliminating an important source of clinical heterogeneity and bias in previous meta-analyses. This increases the external validity and applicability of these results. The review process and quality assessment was conducted in accordance with the Cochrane Collaboration's recommended standard methodology, and following the principles of the PRISMA guidelines[64], including those recently published specifically for multiple-treatments meta-analysis[65].

There are some potential limitations to this study. The validity of the results of any meta-analysis is dependent to a large degree on the quality of included trials, and most trials

were of low to moderate quality, with the risk of performance and selection bias being a particular concern. A lack of well designed, placebo-controlled trials, in particular, led to the combination of placebo and water into one group for the main analysis. This issue was addressed through sensitivity analysis by splitting the groups, which did not show significantly different results.

There was evidence of moderate statistical heterogeneity, and inconsistency between the direct and indirect evidence for some outcomes. This is to be expected given the heterogeneity in trial design, endpoints measured and clinical settings. Nevertheless, subgroup and sensitivity analyses to explore this heterogeneity did not reveal significantly different results.

Comparisons involving low-dose carbohydrate administration for some outcomes were informed by only one or two head-to-head RCTs, with the majority of data coming from indirect evidence. Although this may affect the power and reliability of those effect estimates[9], all of the results for high-dose carbohydrate administration were comparable, suggesting that the true effect of low-dose carbohydrate administration is likely to be similar to the estimates of this multiple-treatments meta-analysis.

Current anaesthetic guidelines[66,67] recommend allowing patients clear fluids for up to 2 h before surgery, based on the established safety of this practice in patients who are not at high risk of aspiration[68]. Recently published ERAS guidelines strongly recommend the routine use of oral carbohydrate loading before a variety of elective procedures, including colonic resection[69], rectal/pelvic surgery[70], gastrectomy[71], pancreaticoduodenectomy[72] and radical cystectomy[73]. This is despite an acknowledgement that the evidence supporting this recommendation is of low to moderate quality, and for some procedures only by extrapolation[71–73]. This review, incorporating the results of more than 40 RCTs and involving over 3000 patients, shows that the administration of preoperative carbohydrate within 4 h of surgery start time is safe, but does not provide a significant clinical benefit over water, or a flavoured drink with no calories. This needs to be considered when developing elective ERAS protocols, particularly given the significant costs involved in routine carbohydrate loading. Future trials investigating preoperative loading should focus on the potential role of other additives, such as immunonutrients, in selected patients.

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References

1 Gouvas N, Tan E, Windsor A, Xynos E, Tekkis PP. Fast-track vs standard care in colorectal surgery: a meta-analysis update. *Int J Colorectal Dis* 2009; **24**: 1119–1131.
2 Lubowski DZ. Enhanced recovery after surgery and laparoscopic colorectal surgery: where to now? *ANZ J Surg* 2014; **84**: 500–501.
3 Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc Nutr Soc* 2002; **61**: 329–336.
4 Nygren J. The metabolic effects of fasting and surgery. *Best Pract Res Clin Anaesthesiol* 2006; **20**: 429–438.
5 Awad S, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. *Clin Nutr* 2013; **32**: 34–44.
6 Li L, Wang Z, Ying XJ, Tian JH, Sun TT, Kang Y *et al.* Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis. *Surg Today* 2012; **42**: 613–624.
7 Smith MD, McCall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database Syst Rev* 2014; (8)CD009161.
8 Zargar-Shoshtari K, Hill AG. Optimization of perioperative care for colonic surgery: a review of the evidence. *ANZ J Surg* 2008; **78**: 13–23.
9 Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ* 2013; **346**: f2914.
10 Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; **331**: 897–900.
11 Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002; **21**: 2313–2324.

12 Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* (5·1.0 edn). The Cochrane Collaboration: London, 2011.
13 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13.
14 StataCorp. *Stata/IC 13·1 for Windows* (13·1 edn). StataCorp: College Station, 2014.
15 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013; **8**: e76654.
16 White IR. Network meta-analysis. *Stata J* 2015; **15**: 951–985.
17 Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 1: Introduction to Evidence Synthesis for Decision Making*; 2012. http://www.nicedsu.org.uk/TSD1%20Introduction.final.08·05.12.pdf [accessed 15 January 2016].
18 An GQ, Zhao XL, Gao YC, Wang GY, Yu YM. Effects of preoperative carbohydrate loading on the changes in serum tumor necrosis factor receptors 1 and 2 and insulin resistance in patients of colon carcinoma. *Natl Med J China* 2008; **88**: 2041–2044.
19 Aronsson A, Al-Ani NA, Brismar K, Hedstrom M. A carbohydrate-rich drink shortly before surgery affected IGF-I bioavailability after a total hip replacement. A double-blind placebo controlled study on 29 patients. *Aging Clin Exp Res* 2009; **21**: 97–101.
20 Asakura A, Mihara T, Goto T. The effect of preoperative oral carbohydrate or oral rehydration solution on postoperative quality of recovery: a randomized, controlled clinical trial. *PLoS One* 2015; **10**: e0133309.
21 Bisgaard T, Kristiansen VB, Hjortso NC, Jacobsen LS, Rosenberg J, Kehlet H. Randomized clinical trial comparing an oral carbohydrate beverage with placebo before laparoscopic cholecystectomy. *Br J Surg* 2004; **91**: 151–158.
22 Braga M, Bissolati M, Rocchetti S, Beneduce A, Pecorelli N, Di Carlo V. Oral preoperative antioxidants in pancreatic surgery: a double-blind, randomized, clinical trial. *Nutrition* 2012; **28**: 160–164.
23 Breuer JP, von Dossow V, von Heymann C, Griesbach M, von Schickfus M, Mackh E *et al.* Preoperative oral carbohydrate administration to ASA III–IV patients undergoing elective cardiac surgery. *Anesth Analg* 2006; **103**: 1099–1108.
24 Canbay Ö, Adar S, Karagöz AH, Çelebi N, Bilen CY. Effect of preoperative consumption of high carbohydrate drink (Pre-Op) on postoperative metabolic stress reaction in patients undergoing radical prostatectomy. *Int Urol Nephrol* 2014; **46**: 1329–1333.
25 Chen J, Cheng L, Xie Z, Li Z. The effect of the preoperative oral intake of 10% glucose solution on postoperative insulin resistance in patients undergoing gastric cancer resection. *J Pract Med* 2014; **30**: 1562–1565.
26 Chen J, Cheng L, Xie Z, Li Z. Impact of preoperative oral liquid carbohydrate on postoperative insulin resistance in gastric cancer patients and its associated study. *Zhonghua Wei Chang Wai Ke Za Zhi* 2015; **18**: 1256–1260.
27 Dock-Nascimento DB, de Aguilar-Nascimento JE, Magalhaes Faria MS, Caporossi C, Slhessarenko N, Waitzberg DL. Evaluation of the effects of a preoperative 2-hour fast with maltodextrine and glutamine on insulin resistance, acute-phase response, nitrogen balance, and serum glutathione after laparoscopic cholecystectomy: a controlled randomized trial. *JPEN J Parenter Enteral Nutr* 2012; **36**: 43–52.
28 Faria MS, de Aguilar-Nascimento JE, Pimenta OS, Alvarenga LC Jr, Dock-Nascimento DB, Slhessarenko N. Preoperative fasting of 2 hours minimizes insulin resistance and organic response to trauma after video-cholecystectomy: a randomized, controlled, clinical trial. *World J Surg* 2009; **33**: 1158–1164.
29 Feguri GR, Lima PR, Lopes AM, Roledo A, Marchese M, Trevisan M *et al.* Clinical and metabolic results of fasting abbreviation with carbohydrates in coronary artery bypass graft surgery. *Rev Bras Cir Cardiovasc* 2012; **27**: 7–17.
30 Harsten A, Hjartarson H, Toksvig-Larsen S. Total hip arthroplasty and perioperative oral carbohydrate treatment: a randomised, double-blind, controlled trial. *Eur J Anaesthesiol* 2012; **29**: 271–274.
31 Hausel J, Nygren J, Thorell A, Lagerkranser M, Ljungqvist O. Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. *Br J Surg* 2005; **92**: 415–421.
32 Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. *Acta Anaesthesiol Scand* 2003; **47**: 191–199.
33 Itou K, Fukuyama T, Sasabuchi Y, Yasuda H, Suzuki N, Hinenoya H *et al.* Safety and efficacy of oral rehydration therapy until 2 h before surgery: a multicenter randomized controlled trial. *J Anesth* 2012; **26**: 20–27.
34 Jarvela K, Maaranen P, Sisto T. Pre-operative oral carbohydrate treatment before coronary artery bypass surgery. *Acta Anaesthesiol Scand* 2008; **52**: 793–797.
35 Karlsson A, Wendel K, Polits S, Gislason H, Hedenbro JL. Preoperative nutrition and postoperative discomfort in an ERAS setting: a randomized study in gastric bypass surgery. *Obes Surg* 2016; **26**: 743–748.
36 Kaska M, Grosmanova T, Havel E, Hyspler R, Petrova Z, Brtko M *et al.* The impact and safety of preoperative oral or intravenous carbohydrate administration *versus* fasting in colorectal surgery – a randomized controlled trial. *Wien Klin Wochenschr* 2010; **122**: 23–30.
37 Lauwick SM, Kaba A, Maweja S, Hamoir EE, Joris JL. Effects of oral preoperative carbohydrate on early postoperative outcome after thyroidectomy. *Acta Anaesthesiol Belg* 2009; **60**: 67–73.
38 Lidder P, Thomas S, Fleming S, Hosie K, Shaw S, Lewis S. A randomized placebo controlled trial of preoperative

carbohydrate drinks and early postoperative nutritional supplement drinks in colorectal surgery. *Colorectal Dis* 2013; **15**: 737–745.
39 Ljunggren S, Hahn RG. Oral nutrition or water loading before hip replacement surgery; a randomized clinical trial. *Trials* 2012; **13**: 97.
40 Ljunggren S, Hahn RG, Nystrom T. Insulin sensitivity and beta-cell function after carbohydrate oral loading in hip replacement surgery: a double-blind, randomised controlled clinical trial. *Clin Nutr* 2014; **33**: 392–398.
41 Ljungqvist O, Thorell A, Gutniak M, Haggmark T, Efendic S. Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. *J Am Coll Surg* 1994; **178**: 329–336.
42 Mathur S, Plank LD, McCall JL, Shapkov P, McIlroy K, Gillanders LK *et al.* Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. *Br J Surg* 2010; **97**: 485–494.
43 Meisner M, Ernhofer U, Schmidt J. Liberalisation of preoperative fasting guidelines: effects on patient comfort and clinical practicability during elective laparoscopic surgery of the lower abdomen. *Zentralbl Chir* 2008; **133**: 479–485.
44 Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis* 2006; **8**: 563–569.
45 Ozdemir F, Eti Z, Dincer P, Gogus FY, Bekiroglu N. The effect of preoperative oral carbohydrate loading on stress response in patients undergoing major or minor surgery. *Turkiye Klinikleri Tip Bilimleri Dergisi* 2011; **31**: 1392–1400.
46 Perrone F, da-Silva AC, Adorno IF, Anabuki NT, Leal FS, Colombo T *et al.* Effects of preoperative feeding with a whey protein plus carbohydrate drink on the acute phase response and insulin resistance. A randomized trial. *Nutr J* 2011; **10**: 66.
47 Pexe-Machado PA, de Oliveira BD, Dock-Nascimento DB, de Aguilar-Nascimento JE. Shrinking preoperative fast time with maltodextrin and protein hydrolysate in gastrointestinal resections due to cancer. *Nutrition* 2013; **29**: 1054–1059.
48 Raksakietisak M, Chinachoti T, Iamaroon A, Thabpenthai Y, Halilamien P, Siriratwarangkul S *et al.* Oral rehydration with 10% carbohydrate drink for preventing postoperative nausea and vomiting (PONV) after low dose of spinal morphine. *J Med Assoc Thai* 2014; **97**: 530–535.
49 Rapp-Kesek D, Stridsberg M, Andersson LG, Berne C, Karlsson T. Insulin resistance after cardiopulmonary bypass in the elderly patient. *Scand Cardiovasc J* 2007; **41**: 102–108.
50 Sada F, Krasniqi A, Hamza A, Gecaj-Gashi A, Bicaj B, Kavaja F. A randomized trial of preoperative oral carbohydrates in abdominal surgery. *BMC Anesthesiol* 2014; **14**: 93.
51 Singh BN, Dahiya D, Bagaria D, Saini V, Kaman L, Kaje V *et al.* Effects of preoperative carbohydrates drinks on immediate postoperative outcome after day care laparoscopic cholecystectomy. *Surg Endosc* 2015; **29**: 3267–3272.
52 Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. *Am J Physiol Endocrinol Metab* 2001; **280**: E576–E583.
53 Soop M, Nygren J, Thorell A, Weidenhielm L, Lundberg M, Hammarqvist F *et al.* Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. *Clin Nutr* 2004; **23**: 733–741.
54 Tran S, Wolever TM, Errett LE, Ahn H, Mazer CD, Keith M. Preoperative carbohydrate loading in patients undergoing coronary artery bypass or spinal surgery. *Anesth Analg* 2013; **117**: 305–313.
55 Wang ZG, Wang Q, Wang WJ, Qin HL. Randomized clinical trial to compare the effects of preoperative oral carbohydrate *versus* placebo on insulin resistance after colorectal surgery. *Br J Surg* 2010; **97**: 317–327.
56 Yang Y, Yan-Bing Z, Xue-Long J, Dong C, Zhi-Hao W. Effects and safety of preoperative oral carbohydrate in radical distal gastrectomy – a randomized clinical trial. *J Cancer Sci Ther* 2012; **4**: 116–119.
57 Yildiz H, Gunal SE, Yilmaz G, Yucel S. Oral carbohydrate supplementation reduces preoperative discomfort in laparoscopic cholecystectomy. *J Invest Surg* 2013; **26**: 89–95.
58 Yilmaz N, Cekmen N, Bilgin F, Erten E, Ozhan MO, Cosar A. Preoperative carbohydrate nutrition reduces postoperative nausea and vomiting compared to preoperative fasting. *J Res Med Sci* 2013; **18**: 827–832.
59 Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively – a randomised clinical trial. *Clin Nutr* 2005; **24**: 32–37.
60 Zelic M, Stimac D, Mendrila D, Tokmadzic VS, Fisic E, Uravic M *et al.* Influence of preoperative oral feeding on stress response after resection for colon cancer. *Hepatogastroenterology* 2012; **59**: 1385–1389.
61 Harbord RM, Higgins JPT. Meta-regression in Stata. *Stata J* 2008; **8**: 493–519.
62 Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. *JAMA* 2014; **311**: 405–411.
63 Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr* 1998; **17**: 65–71.
64 Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**: 264–269, W264.
65 Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network

meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162**: 777–784.
66 Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Soreide E *et al.*; European Society of Anaesthesiology. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2011; **28**: 556–569.
67 American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology* 2011; **114**: 495–511.
68 Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. *Cochrane Database Syst Rev* 2003; (4)CD004423.
69 Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N *et al.*; Enhanced Recovery After Surgery (ERAS) Society for Perioperative Care; European Society for Clinical Nutrition and Metabolism (ESPEN); International Association for Surgical Metabolism and Nutrition (IASMEN). Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 259–284.
70 Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN *et al.*; Enhanced Recovery After Surgery (ERAS) Society for Perioperative Care; European Society for Clinical Nutrition and Metabolism (ESPEN); International Association for Surgical Metabolism and Nutrition (IASMEN). Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 285–305.
71 Mortensen K, Nilsson M, Slim K, Schafer M, Mariette C, Braga M *et al.*; Enhanced Recovery After Surgery (ERAS®) Group. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Br J Surg* 2014; **101**: 1209–1229.
72 Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schafer M *et al.*; ERAS® Society; European Society for Clinical Nutrition and Metabolism; International Association for Surgical Metabolism and Nutrition. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS) Society recommendations. *Clin Nutr* 2012; **31**: 817–830.
73 Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M *et al.* Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr* 2013; **32**: 879–887.

Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Further methodological details (Word document)

Appendix S2 Additional results for secondary outcomes (Word document)

Table S1 Details of included studies (Word document)

Fig. S1 Risk-of-bias table, showing the domain assessment for individual trials (Word document)

Fig. S2 Cumulative meta-analysis of trials reporting comparison of high-dose carbohydrate *versus* fasting or water/placebo (control) with regard to length of postoperative hospital stay (Word document)

Fig. S3 Comparison-adjusted funnel plot for length of postoperative stay (Word document)

A2 Registered review protocol – Surgical management of gastro-oesophageal reflux disease (GORD) in adults: a systematic review and network meta-analysis

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Surgical management of gastro-oesophageal reflux disease (GORD) in adults: a systematic review and network meta-analysis

Mohammad A Amer, Mark D Smith, G Peter Herbison, John L McCall

Citation

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Review question

To compare the effectiveness of the various surgical fundoplication techniques on the outcomes of GORD-related symptoms, postoperative side effects and quality of life in adults undergoing surgery for the treatment of GORD.

Searches

Electronic searches:
The following databases will be searched to identify eligible studies for this review:
1. The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, most recent issue).
2. MEDLINE (1966 to current).
3. EMBASE (1980 to current).
4. Web of Science (1945 to current).
Language restrictions will not be applied. The search strategy will be developed using a combination of subject headings and free text terms relating to the surgical treatment of GORD, in consultation with an expert health librarian. The Cochrane sensitivity maximising search strategy will be used to search for RCTs in MEDLINE. The BMJ's EMBASE Randomised Controlled Trial Strategy will be used to search for RCTs in EMBASE.
Searching other resources:
The World Health Organisation's International Clinical Trials Registry Platform and clinicaltrials.gov will be searched to identify ongoing trials. The contact authors for any such trials will then be approached by letter or email requesting any available information to date (MAA).
The reference lists of all eligible studies and of reviews of the topic will be hand-searched to identify any additional studies. Experts in the field will also be contacted to identify any unpublished research or ongoing trials.
The CENTRAL search will include the Cochrane Upper Gastrointestinal and Pancreatic Disease Group Specialised Register, which incorporates the Group's hand-searching results of relevant journals and conference proceedings in the field.

Types of study to be included

We will include all randomised and quasi-randomised clinical trials (RCTs) that compare different fundoplication techniques for the treatment of GORD. Trials that compare a fundoplication technique with best medical treatment with PPIs will also be included. We will include studies that used an open or laparoscopic approach. Trials comparing fundoplication techniques specifically in the context of management for established Barrett's, or exclusively for extra-oesophageal manifestations will be excluded, as these will incur different key indications for surgery and outcomes of interest. There will be no language, publication status, or year of publication restrictions. We will not exclude studies if they do not report either of the primary outcomes, as these will be used in the secondary outcome analysis and/or the narrative review. Trials assessing endoscopic treatment of GORD will be excluded. Non-randomised studies will be excluded, as they carry an increased risk of bias. Authors of published trials will be contacted for clarification if

randomisation status is not clear.

Condition or domain being studied
Gastro-oesophageal reflux disease. Fundoplication.

Participants/population
All adults with an established diagnosis of GORD, based on symptoms and an objective measure such as endoscopy or pH manometry, deemed appropriate for surgical management.

Intervention(s), exposure(s)
The interventions will include any fundoplication technique, whether performed by open or laparoscopic surgery. The intervention groups for the main analysis will be as follows:
1. Total (360 degree) fundoplication (with or without the division of the short gastric arteries)
2. 90 degree fundoplication
3. Anterior partial fundoplication (120 degree or more)
4. Posterior partial fundoplication (180 degree, 270 degree)
5. Medical treatment with PPIs (as a comparator)
Each of these techniques will be analysed as an independent intervention in the network. Interventions which include other variations such as variable wrap lengths, omission of a hiatoplasty or fixation to the right hiatal pillar as part of the procedure, or the non-use of a bougie will be permitted, but such variations will be noted. Interventions involving fundoplication in combination with another procedure (such as Heller's myotomy for achalasia) will be excluded.

Comparator(s)/control
Medical treatment with PPIs (as a comparator).
See 'types of interventions' above.

Context

Primary outcome(s)
1. Health-related quality of life scores, measured on an appropriate validated tool.
2. GORD-specific quality of life, measured on an appropriate validated tool.
3. Dysphagia, measured either as a dichotomous variable or on a validated scale (such as a Dakkak score).
For primary outcomes, data will be analysed separately in four groups according to follow-up time:
a. From 3 months, up to and including 1 year
b. From over 1 year, up to and including 5 years
c. From over 5 years, up to and including 10 years
d. Over 10 years
Where one trial has reported the same primary outcome for different follow-up time-points, we will include the data in the appropriate groups, ensuring that duplication is avoided.

Secondary outcome(s)
1. Reflux symptoms. We anticipate that most studies will report this as a dichotomous or categorical scale patient-reported outcome.
2. Oesophageal acid exposure, measured as a DeMeester score.
3. Total oesophageal acid exposure time (as a percentage) on pH monitoring.
4. Dilatation for dysphagia rate, defined as the need for oesophageal dilatation for symptomatic dysphagia postoperatively.
5. Reoperation rate, defined as the number of patients who required revision surgery for ongoing symptoms and/or objective findings of persistent GORD during the follow-up period.
6. Postoperative complications, as defined by the trial authors.
7. Gas bloat, measured on a dichotomous, categorical or visual scale.
For all secondary outcomes except postoperative complications, data will be analysed separately in four groups according to follow-up time, where enough data is available to make this meaningful:

a. From 3 months, up to and including 1 year.
b. From over 1 year, up to and including 5 years.
c. From over 5 years, up to and including 10 years.
d. Over 10 years.
Where one trial has reported the same secondary outcome for different follow-up time-points, we will include the data in the appropriate groups, ensuring that duplication is avoided.

Data extraction (selection and coding)

Selection of studies:
The results of searches from both the electronic databases and other resources will be combined in a spreadsheet. Duplicate citation records will be excluded. Duplicate publications will be retained in case all data are not reported in both. Two authors (MAA and JLM) will independently screen all titles and abstracts for eligibility. The full text of potentially eligible trials will then be obtained and reviewed against the pre-defined inclusion criteria. Any exclusions at this point will be independently recorded (together with the reason for exclusion), before a final list of included trials is drawn up. Disagreement will be resolved by discussion and consensus. Failing this, a third author (GPH) will arbitrate. Study selection will be reported as a PRISMA flow chart.
Data extraction and management:
A pre-piloted data extraction form, based on the Cochrane Collaboration's Data Collection Form Template will be used by two authors (MAA and MDS) to independently extract and record data. Discrepancies will be resolved by discussion, or if a consensus cannot be reached, discussion with a third author (GPH). Any requests for further data will be made if required (MAA), by contacting the first or contact author of the relevant trial, where an email address is available.
Dealing with missing data:
Where data are missing or not available, we will contact the study authors to request this (MAA), where an email address is available. Where data are missing to the extent that the study cannot be included in the meta-analysis and attempts to obtain the relevant data have been exhausted, the results will be presented and discussed in the review, in the context of the findings.
We will calculate missing statistics such as standard deviations from the reported data where possible. Where standard deviations cannot be calculated, we will impute these using the mean of the reported standard deviations from the other trials. Sensitivity analysis will be performed to explore the effect of imputed versus reported data.

Risk of bias (quality) assessment

The methodological quality of each included study will be independently assessed by two authors (MAA and MDS), using a standardised, pre-piloted form as part of the data extraction process. The assessment will be based on the Cochrane Collaboration's Risk of Bias tool, using the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and any other potential sources of bias. Each domain will be assessed as low risk, high risk, or unclear. Disagreements will be resolved by discussion; and arbitration by a third author (GPH) where consensus cannot be reached. We will report the results of this assessment as a Risk of Bias summary figure.

Strategy for data synthesis

Data synthesis:
A network, or multiple treatments, meta-analysis will be performed to use the available indirect evidence, in addition to the pair-wise comparisons. This is a method of synthesising information from a network of trials addressing the same question using different interventions, where both the direct (pair-wise) and indirect evidence can be used to produce a single effect size. This increases precision while randomisation is respected. This also enables a ranking of the different interventions according to their effectiveness, as measured by different outcomes. This will be performed within a frequentist framework using Stata, by running the routines available for network meta-analysis. The construct of the network will be reported as a network geometry figure.

Assessment of heterogeneity:
We will assess the heterogeneity of included studies according to their clinical, methodological and statistical diversity. Clinical heterogeneity will be assessed using subgroup analysis. Statistical heterogeneity will be assessed by calculating predictive intervals. We will also assess inconsistency or incoherence of each independent three-way loop in the evidence structure, by calculating the difference between the direct and indirect estimates (the inconsistency factor) in each closed loop formed by the network of trials. This will be presented as an inconsistency plot. Any significant inconsistencies will be investigated further to determine possible causes, including methodological and clinical heterogeneity.
Assessment of reporting biases:
We will assess publication bias by visual inspection of a funnel plot if there are enough studies to make this reasonable.

Analysis of subgroups or subsets

Subgroup analysis:
We will perform the following subgroup analyses if possible:
1. Open versus laparoscopic surgery (per intervention technique).
2. Division of the short gastric arteries in 360o wraps.
Sensitivity analysis:
We will conduct sensitivity analysis by excluding trials of low methodological quality and consider the results of this analysis in comparison to overall findings in the discussion section. We will also conduct sensitivity analysis to explore the effects of imputed data; and the effects of studies where more than one technique was used in the same arm.

Contact details for further information

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Conflicts of interest

None known

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A3 Network meta-analysis of surgical management of gastro-oesophageal reflux disease in adults

Systematic review

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 world[1]. Proton pump inhibitor (PPI) therapy has been the mainstay of treatment for the past 20 years, with surgery reserved mainly for patients with refractory GORD[2]. 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) fundoplication[9], 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 control[10].

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 published[18], to determine which fundoplication technique is superior, both in terms of reflux control and potential harms[19]. Calls have been made for even more RCTs[20], whereas others have suggested that none of the options is ideal[21], and the choice of procedure should simply be left to the surgeon[10].

Network meta-analysis allows the simultaneous comparison of multiple different treatments for a given condition, while respecting randomization[22]. 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 RCT[23]. 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 methodology[24] and the PRISMA guidelines[25], including those specifically concerning network meta-analysis[26]. 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 tool[28] 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

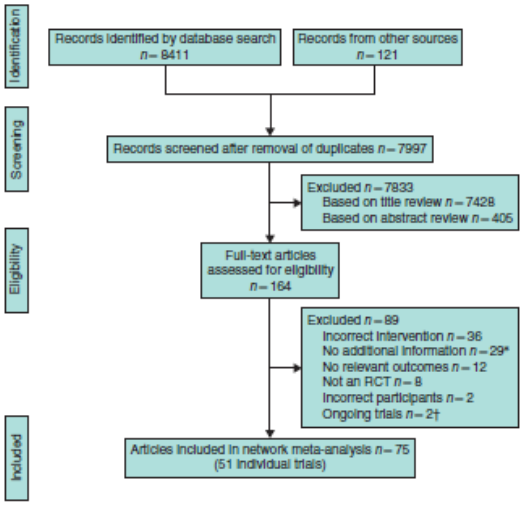

Fig. 1 PRISMA flow chart showing selection of articles for review. *Includes duplicate publications and articles reporting results for an included trial with no additional relevant data. †No data currently available from trial investigators

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 rankogram[29]. 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 *versus* PPF	19	2153	1989–2015	14	2		3
Nissen *versus* APF	6	530	2004–2016	3		1	2
Nissen *versus* 90°	3	225	1989–2012	1		2	
Nissen *versus* PPI	3	803	2008–2011	2	1		
PPF *versus* APF	4	339	2007–2017	3		1	
PPF *versus* 90°	1	32	1989	1			
Nissen *versus* Angelchik	3	163	1984–1994	3			
Nissen *versus* Hill	2	132	1974–2012		2		
Nissen *versus* other§	7	706	1974–2015	4	3		
PPF *versus* FND 360°	1	252	2012		1		
NSGVD *versus* NSGVP	6	438	1999–2009	4	1	1	
Bougie *versus* no bougie¶	1	171	2000		1		
BM IV *versus* 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 hiatoplasty, Nissen with fascial graft, fixed 'non-deformable' 360° fundoplication (FND), mesh hiatoplasty 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.

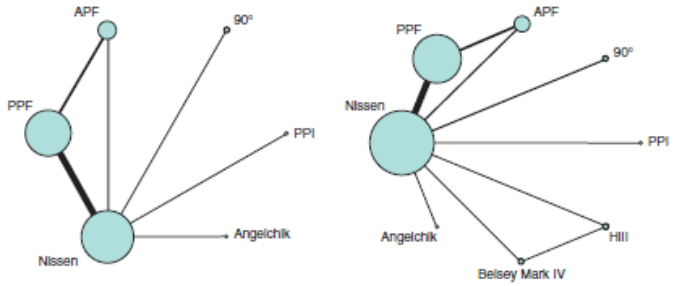

Fig. 2 Network maps of direct evidence for **a** short-term reflux and **b** dysphagia rate at 3–12 months after treatment. The size of each circle (node) is proportional to the number of patients who received the treatment. The width of the lines represents the number of RCTs that directly compared 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

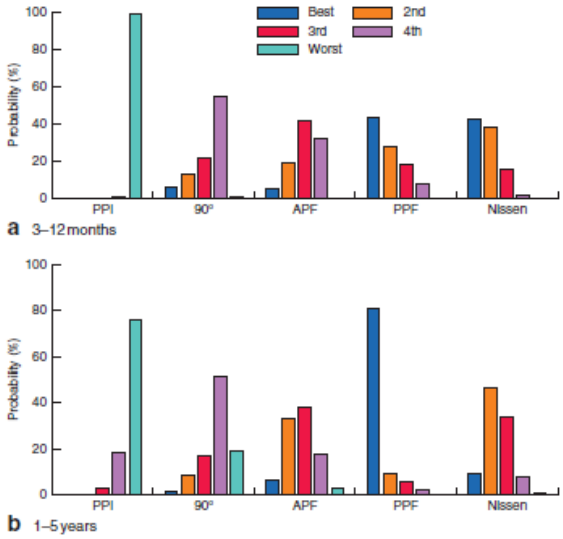

Fig. 3 Rankograms of fundoplications according to reflux scores at **a** 3–12 months and **b** 1–5 years after treatment. The probability of each fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is shown. There were insufficient data for ranking at 5–10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

statistically significant differences between the fundoplications. Both NF and PPF had significantly lower reflux scores than mesh hiatoplasty with cardiophrenicopexy. *Fig. 3a* shows the fundoplication 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 fundoplication in comparison with PPI, except 90°. PPF alone had statistically significantly lower reflux scores compared with mesh hiatoplasty with cardiophrenicopexy. Fundoplication 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

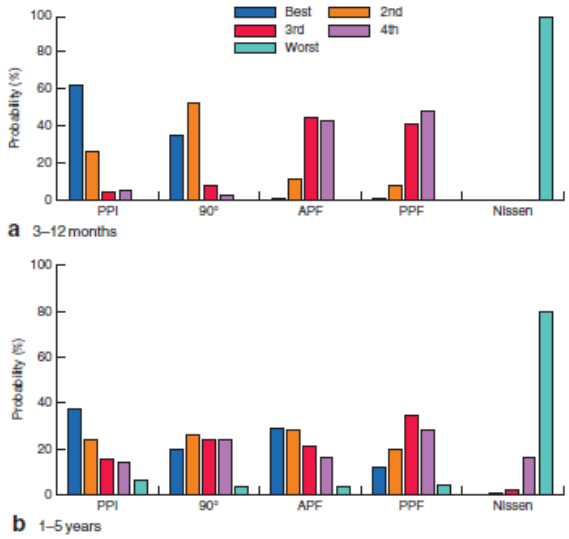

Fig. 4 Rankograms of fundoplications according to dysphagia rate at **a** 3–12 months and **b** 1–5 years after treatment. The probability of each fundoplication ranking as the best, second best, third, fourth or worst treatment in the network is shown. There were insufficient data for ranking at 5–10 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 fundoplications, 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).

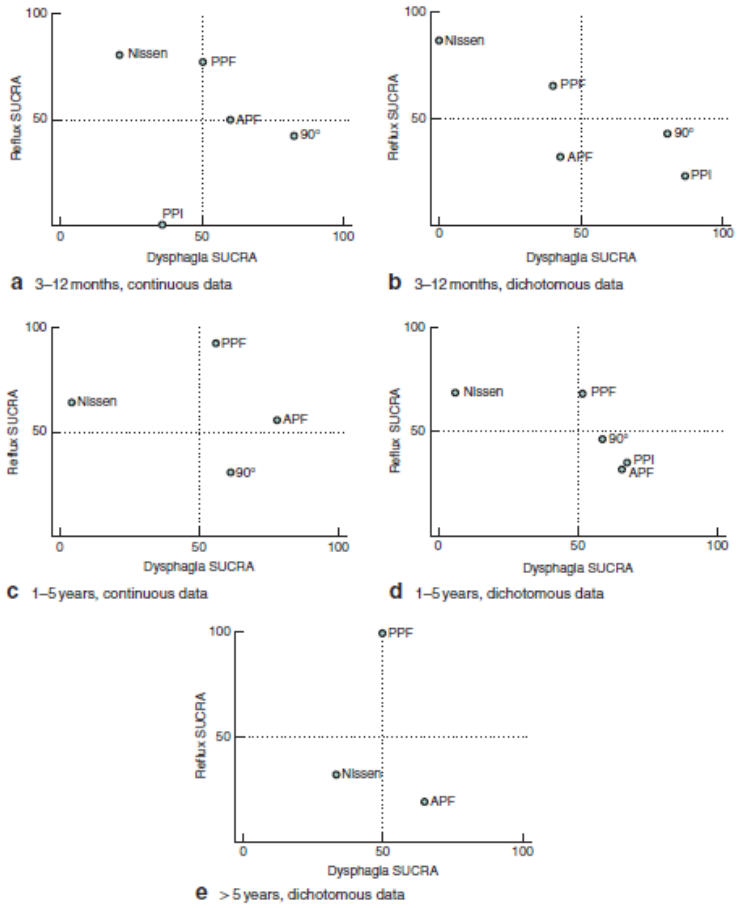

Fig. 5 Clustered ranking plots of main treatments at different time points, according to efficacy of reflux control and incidence of dysphagia: **a** 3–12-month continuous data; **b** 3–12-month dichotomous data; **c** 1–5-year continuous data; **d** 1–5-year dichotomous data; **e** more than 5-year 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 compare[20]. 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 compared[20]. 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 time[19].

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 randomization[22]. 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 procedures[4]. More objective tools such as pH monitoring and oesophagoscopy have traditionally been regarded as the standard methods of assessing reflux control after surgery for GORD[18], and manometry and mechanical studies have been used to assess side-effects such as dysphagia[31]. 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 results[36].

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 severity[35]. Patient-reported symptom scores have been shown to correlate best with the actual outcome as perceived by the patient[37].

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 concerns[38], 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 US[10] and European[19] 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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Disclosure: The authors declare no conflict of interest.

References

1 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**: 710–717.
2 Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical *versus* surgical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2010; (3)CD003243.
3 Broeders JA, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG *et al.* Systematic review and meta-analysis of laparoscopic Nissen (posterior total) *versus* Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2010; **97**: 1318–1330.
4 Grant AM, Cotton SC, Boachie C, Ramsay CR, Krukowski ZH, Heading RC *et al.*; REFLUX Trial Group. Minimal access surgery compared with medical management for gastro-oesophageal reflux disease: five year follow-up of a randomised controlled trial (REFLUX). *BMJ* 2013; **346**: f1908.
5 Faria R, Bojke L, Epstein D, Corbacho B, Sculpher M; REFLUX trial group. Cost-effectiveness of laparoscopic fundoplication *versus* continued medical management for the treatment of gastro-oesophageal reflux disease based on long-term follow-up of the REFLUX trial. *Br J Surg* 2013; **100**: 1205–1213.
6 Anvari M, Allen C, Marshall J, Armstrong D, Goeree R, Ungar W *et al.* A randomized controlled trial of laparoscopic Nissen fundoplication *versus* proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. *Surg Endosc* 2011; **25**: 2547–2554.
7 Goeree R, Hopkins R, Marshall JK, Armstrong D, Ungar WJ, Goldsmith C *et al.* Cost–utility of laparoscopic Nissen fundoplication *versus* proton pump inhibitors for chronic and controlled gastroesophageal reflux disease: a 3-year prospective randomized controlled trial and economic evaluation. *Value Health* 2011; **14**: 263–273.
8 Mackay C, Wileman SM, Krukowski ZH, Bruce J. Laparoscopic fundoplication for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2010; (9)CD008719.
9 Nissen R. [A simple operation for control of reflux esophagitis.] *Schweiz Med Wochenschr* 1956; **86**(Suppl 20): 590–592.
10 Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD; SAGES Guidelines Committee. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 2647–2669.
11 Ma S, Qian B, Shang L, Shi R, Zhang G. A meta-analysis comparing laparoscopic partial *versus* Nissen fundoplication. *ANZ J Surg* 2012; **82**: 17–22.
12 Memon MA, Subramanya MS, Hossain MB, Yunus RM, Khan S, Memon B. Laparoscopic anterior *versus* posterior fundoplication for gastro-esophageal reflux disease: a meta-analysis and systematic review. *World J Surg* 2015; **39**: 981–996.
13 Broeders JA, Roks DJ, Ahmed Ali U, Draaisma WA, Smout AJ, Hazebroek EJ. Laparoscopic anterior *versus* posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg* 2011; **254**: 39–47.
14 Varin O, Velstra B, De Sutter S, Ceelen W. Total *vs* partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. *Arch Surg* 2009; **144**: 273–278.
15 Broeders JA, Roks DJ, Ahmed Ali U, Watson DI, Baigrie RJ, Cao Z *et al.* Laparoscopic anterior 180-degree *versus* Nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg* 2013; **257**: 850–859.
16 Shan CX, Zhang W, Zheng XM, Jiang DZ, Liu S, Qiu M. Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. *World J Gastroenterol* 2010; **16**: 3063–3071.
17 Tan G, Yang Z, Wang Z. Meta-analysis of laparoscopic total (Nissen) *versus* posterior (Toupet) fundoplication for gastro-oesophageal reflux disease based on randomized clinical trials. *ANZ J Surg* 2011; **81**: 246–252.
18 Demeester TR, Johnson LF, Kent AH. Evaluation of current operations for the prevention of gastroesophageal reflux. *Ann Surg* 1974; **180**: 511–525.

19 Fuchs KH, Babic B, Breithaupt W, Dallemagne B, Fingerhut A, Furnee E *et al.*; European Association of Endoscopic Surgery (EAES). EAES recommendations for the management of gastroesophageal reflux disease. *Surg Endosc* 2014; **28**: 1753–1773.
20 Thompson SK, Watson DI. What is the best anti-reflux operation? All fundoplications are not created equal. *World J Surg* 2015; **39**: 997–999.
21 Daud WN, Thompson SK, Jamieson GG, Devitt PG, Martin IJ, Watson DI. Randomized controlled trial of laparoscopic anterior 180° partial *versus* posterior 270° partial fundoplication. *ANZ J Surg* 2015; **85**: 668–672.
22 Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; **331**: 897–900.
23 Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002; **21**: 2313–2324.
24 Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. http://handbook-5-1.cochrane.org/ [accessed 4 June 2017].
25 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535.
26 Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162**: 777–784.
27 Amer MA, Smith MD, Herbison GP, McCall JL. *Surgical Management of Gastro-Oesophageal Reflux Disease (GORD) in Adults: A Systematic Review and Network Meta-analysis*. PROSPERO 2014: CRD42014010074. http://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=10074&VersionID=51607 [accessed 15 June 2018].
28 Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD *et al.*; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
29 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013; **8**: e76654.
30 White IR. Network meta-analysis. *Stata J* 2015; **15**: 951–985.
31 Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) *versus* posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**: 57–63.
32 Mathew G, Watson DI, Myers JC, Holloway RH, Jamieson GG. Oesophageal motility before and after laparoscopic Nissen fundoplication. *Br J Surg* 1997; **84**: 1465–1469.
33 Walker SJ, Holt S, Sanderson CJ, Stoddard CJ. Comparison of Nissen total and Lind partial transabdominal fundoplication in the treatment of gastro-oesophageal reflux. *Br J Surg* 1992; **79**: 410–414.
34 O'Boyle CJ, Watson DI, Jamieson GG, Myers JC, Game PA, Devitt PG. Division of short gastric vessels at laparoscopic Nissen fundoplication: a prospective double-blind randomized trial with 5-year follow-up. *Ann Surg* 2002; **235**: 165–170.
35 Shaw JM, Bornman PC, Callanan MD, Beckingham IJ, Metz DC. Long-term outcome of laparoscopic Nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: a prospective, randomized trial. *Surg Endosc* 2010; **24**: 924–932.
36 Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen *versus* anterior 180°partial fundoplication. *Br J Surg* 2008; **95**: 1501–1505.
37 Watson DI, Devitt PG, Smith L, Jamieson GG. Anterior 90° partial vs Nissen fundoplication – 5 year follow-up of a single-centre randomised trial. *J Gastrointest Surg* 2012; **16**: 1653–1658.
38 Kmiot WA, Kirby RM, Akinola D, Temple JG. Prospective randomized trial of Nissen fundoplication and Angelchik prosthesis in the surgical treatment of medically refractory gastro-oesophageal reflux disease. *Br J Surg* 1991; **78**: 1181–1184.

Supporting information

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

APPENDIX B

Preoperative carbohydrate loading systematic review and NMA – additional material

B1 Search strategies

CENTRAL search

#1 MeSH descriptor Carbohydrates explode all trees

#2 ((carbohydrat* or CHO) near (oral or load* or treatment or drink* or fluid* or administrat* or rich))

#3 (oral fluid* or CHO or fasting):ti,ab

#4 nutricia* or maltodextrin

#5 (#1 OR #2 OR #3 OR #4)

#6 MeSH descriptor Postoperative Care, this term only

#7 MeSH descriptor Postoperative Period, this term only

#8 MeSH descriptor Insulin Resistance, this term only

#9 MeSH descriptor Surgical Procedures, Elective, this term only

#10 MeSH descriptor Postoperative Complications, this term only

#11 MeSH descriptor Cholecystectomy, Laparoscopic, this term only

#12 MeSH descriptor Pain, Postoperative, this term only

#13 pre?op*:ti,ab

#14 (postoperative near (recovery or pain or nausea or vomiting or fatigue)):ti,ab

#15 (insulin near resistance):ti,ab

#16 (surgery near (elective or abdominal)):ti,ab

#17 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

#18 (#5 AND #17)

Medline search

1. ((carbohydrat* or CHO) adj3 (oral or load* or treatment or drink* or fluid* or administrat* or rich)).mp. or (oral fluid* or CHO or fasting).ti,ab. or (nutricia* or maltodextrin).mp. or Carbohydrates/

2. Postoperative Care/ or Postoperative Period/ or Insulin Resistance/ or Surgical Procedures, Elective/ or Postoperative Complications/ or Cholecystectomy, Laparoscopic/ or Pain, Postoperative/ or pre?op*.ti,ab. or (post?operative adj3 (recovery or pain or nausea or vomiting or fatigue)).ti,ab. or (insulin adj3 resistance).ti,ab. or (surgery adj3 (elective or abdominal)).ti,ab.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
5. 3 and 4

EMBASE search

1. ((carbohydrat* or CHO) adj3 (oral or load* or treatment or drink* or fluid* or administrat* or rich)).mp. or (oral fluid* or CHO or fasting).ti,ab. or (nutricia* or maltodextrin).mp. or carbohydrate/
2. pre?op*.ti,ab. or (post?operative adj3 (recovery or pain or nausea or vomiting or fatigue)).ti,ab. or (insulin adj3 resistance).ti,ab. or (surgery adj3 (elective or abdominal)).ti,ab. or postoperative care/ or postoperative period/ or postoperative pain/ or insulin resistance/ or elective surgery/ or postoperative complication/ or cholecystectomy/
3. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals.sh not (humans.sh and animals.sh))
4. 3 and 2 and 1

CINAHL search

S1 TX (carbohydrat* or CHO) and AB (oral or load* or treatment or drink* or fluid* or administrat* or rich)
S2 AB oral fluid* or CHO or fasting
S3 TX nutricia* or maltodextrin
S4 (MM “Carbohydrates”)
S5 S1 or S2 or S3 or S4
S6 (MH “Postoperative Pain”) OR (MH “Postoperative Period”) OR (MH “Postoperative Care”) OR (MH “Postoperative Complications”) OR (MH “Insulin Resistance”) OR (MH “Surgery, Elective”) OR (MH “Cholecystectomy, Laparoscopic”)

S7 TI pre?op* or AB pre?op*

S8 AB postoperative and AB (recovery or pain or nausea or vomiting or fatigue)

S9 AB insulin and AB resistance

S10 AB surgery and AB (elective or abdominal)

S11 S6 or S7 or S8 or S9 or S10

S12 S5 and S11

S13 (random* or placebo or trial*) or (((single or double or triple or treble) and (mask* or blind*))) or (multicenter* or prospective)

S14 (MH “Random Assignment”) OR (MH “Clinical Trials”) OR (MH “Placebos”) OR (MH “Double-Blind Studies”) OR (MH “Single-Blind Studies”) OR (MH “Triple-Blind Studies”) OR (MH “Prospective Studies”) OR (MH “Multicenter Studies”)

S15 S13 or S14

S16 S12 and S15

Web of Science search

1. TS=(pre$op*) or TS=((cholecystectomy or surgery or surgical) same (elective or abdominal or laparoscopic))

2. TS=((carbohydrat* or CHO) same (oral or load or treatment or drink* or fluid* or administrat* or rich)) or TS=(nutricia* or maltodextrin)

3. TS=(post$op* same (care or period or complications or pain or recovery or nausea or vomiting or fatigue)) or TS=(insulin same resistance)

4. #1 AND #2 AND #3

B2 Data extraction form

Unique ID	ISDN	First author	Year	Reviewer	Date Reviewed

Notes
Study Methods and Details

Trial Characteristics	Details
Study site(s)	
Country/countries	
How was participant eligibility defined?	
Mean or median age of participants	
Risk breakdown of participants (ASA where defined)	
Surgery type / number	
Number receiving: * Epidural anaesthesia * Spinal anaesthesia * General anaesthesia	
Number undergoing laparoscopic/minimally invasive surgery	
How many participants were randomized?	
Number of participants allocated to: * Carbohydrate * Placebo * Fasting	
Number of participants analysed: * Carbohydrate * Placebo * Fasting	
Carbohydrate group: * Preparation * Time administered * Route administered	

(*Continued*)

* Volume of drink * Carbohydrate dose * Co-intervention	
Placebo group: * Details of placebo * Time administered * Amount of drink * Carbohydrate dose	
Fasting group: * Duration of preop fast - solids * Duration of preop fast - liquids * Duration of preop fast - carbohydrate	

References to other trials

Did this report include any references to published or unpublished trials potentially eligible for this review?	**Yes/No**	No

First author	**Journal/Conference**	**Title**	**Year of publication/presentation**	**Contact details**

Outcomes - Complete a separate copy for each relevant subgroup

Subgroup	**n**

For continuous data:

Out-come	**Unit of mea-sure-ment**	**Carbohydrate group**			**Placebo group**			**Fasting group**			**Details**
		n	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	
Primary outcome - Length											

(*Continued*)

of Hospital Stay											
Insulin resistance (HOMA)											
Insulin resistance (clamp)											
Postop fatigue											
Postop well being											
Postop nausea at 24 hours											
Postop vomiting in the first 24 hours											
Postop time to passage of flatus											
Postop time to passage of first bowel movement											

For dichotomous data:

Outcome	Carbohydrate group		Placebo group		Fasting group		Details
	number with event	number without event	number with event	number without event	number with event	number without event	
Primary outcome - Total complications							
Aspiration pneumonitis							
Postop vomiting 1 or more episodes							

Domain	Describe	Reviewer's Judgement - Risk of Bias
1. Adequate sequence generation	Unclear	
2. Allocation concealment	Unclear	
3. Blinding - Subjective	Unclear	
Blinding - Objective	Unclear	
4. Incomplete outcome data - Length of Stay	Unclear	
Incomplete outcome data - Complication rate	Unclear	
Incomplete outcome data - Secondary endpoints	Unclear	
5. Selective outcome reporting	Unclear	
6. Other potential threats to validity	Unclear	

APPENDIX C

Anti-reflux surgery systematic review and NMA – additional material

C1 Search strategies

CENTRAL search

1. (MeSH descriptor gastroesophageal reflux, explode all trees) or (MeSH descriptor bile reflux, explode all trees) or (MeSH descriptor heartburn, explode all trees) or (MeSH descriptor esophagitis, explode all trees) or (MeSH descriptor gastritis, explode all trees) or (MeSH descriptor gastroparesis, explode all trees) or (MeSH descriptor gastric emptying, explode all trees) or (MeSH descriptor esophageal motility disorders, explode all trees) or (MeSH descriptor dyspepsia, explode all trees) or (MeSH descriptor eructation, explode all trees) or (MeSH descriptor hernia, hiatal, explode all trees) or (esophag* or oesophag*) or (acid regurgitation) or (gastric acid) or (gastr* near reflux):ti,ab or (gord or gerd):ti,ab or (duodenogastric reflux) or (acid near reflux) or (gastr* acid secret*) or (stomach acid secret*) or (gastr* near erosion) or (gastr* near ulcer) or (stomach erosion) or (stomach near ulcer) or (peptic near ulcer) or (heartburn or indigestion) or (esophagitis or oesophagitis) or (les):ti,ab or (low* sphinct* pressure) or (gastr* empt* disorder) or (stomach empt* disorder) or (dyspep*) or (eructat*) or (regurg*)
2. (MeSH descriptor fundoplication, explode all trees) or (fundoplic*):ti,ab or (nissen or rossetti or toupet or lind or watson or belsey or dor or hill procedure):ti,ab or (part* near fundoplication) or (antireflux surg*):ti,ab or (antireflux interven*):ti,ab or (laparosc* near fundoplication) or (open near fundoplication)
3. (#1 and #2)

Medline search

1. (randomized controlled trial or randomised controlled trial or controlled clinical trial).pt or randomized.ti,ab or randomised.ti,ab or placebo.ti,ab or drug therapy.sh or randomly.ti,ab or trial.ti,ab or groups.ti,ab
2. animals.sh NOT humans.sh
3. 1 not 2

4. esophagus/ or gastroesophageal reflux/ or exp laryngopharyngeal reflux/ or duodenogastric reflux/ or bile reflux/ or heartburn/ or esophagitis/ or esophagitis, peptic/ or gastritis/ or exp peptic ulcer/ or gastroparesis/ or gastric emptying/ or dyspepsia/ or eructation/ or exp hernia, diaphragmatic/ or $esophag*.mp or acid regurgitation.mp or (gastr* adj3 reflux).tw or gord.tw or gerd.tw or (acid adj3 reflux).tw or (gastr* adj3 acid adj3 secret*).tw or (stomach adj3 acid adj3 secret*).tw or (gastr* adj3 erosion).tw or (gastr* adj3 ulcer).tw or (stomach adj3 erosion).tw or (stomach adj3 ulcer).tw or (peptic adj3 ulcer).tw or (heartburn or indigestion).tw or $esophagitis.tw or (peptic adj3 $esophagitis).tw or les.tw or (low* adj3 sphincter adj3 pressure).tw or ($esophag* adj3 motil* adj3 disorder).tw or (gastr* adj3 empt* adj3 disorder).tw or (stomach adj3 empt* adj3 disorder).tw or dyspep*.tw or eructat*.tw or regurg*.tw

5. fundoplication/ or gastric fundus/ or fundoplic*.tw or (nissen or rossetti or toupet or lind or watson or belsey or dor or hill procedure).tw or (part* adj3 fundoplication).tw or (antireflux adj3 surg*).tw or (antireflux adj3 interven*).tw or (laparosc* adj3 fundoplication).tw or (open adj3 fundoplication).tw or (minim* adj3 fundoplication).tw

6. 3 and 4 and 5

EMBASE search

1. (random$ or factorial$ or crossover$ or cross-over$ or cross over$ or placebo$ or singl$ adj blind$ or doubl$ adj blind$ or triple blind$ or assign$ or allocate$ or volunteer$).ti,ab or crossover procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/

2. (animal$ not human$).sh,hw

3. (book or conference paper or editorial or letter or review).pt not exp randomized controlled trial/

4. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab not exp randomized controlled trial/

5. 1 not (2 or 3 or 4)

6. esophagus/ or gastroesophageal reflux/ or exp laryngopharyngeal reflux/ or duodenogastric reflux/ or bile reflux/ or heartburn/ or esophagitis/ or esophagitis, peptic/ or gastritis/ or exp peptic ulcer/ or gastroparesis/ or gastric emptying/ or dyspepsia/ or eructation/ or exp hernia, diaphragmatic/ or $esophag*.mp or acid regurgitation.mp or (gastr* adj3 reflux).tw or gord.tw or gerd.tw or (acid adj3 reflux).tw or (gastr* adj3 acid adj3 secret*).tw or (stomach adj3 acid adj3 secret*).tw or (gastr* adj3 erosion).tw or (gastr* adj3 ulcer).tw or (stomach adj3 erosion).tw or

(stomach adj3 ulcer).tw or (peptic adj3 ulcer).tw or (heartburn or indigestion).tw or $esophagitis.tw or (peptic adj3 $esophagitis).tw or les.tw or (low* adj3 sphincter adj3 pressure).tw or ($esophag* adj3 motil* adj3 disorder).tw or (gastr* adj3 empt* adj3 disorder).tw or (stomach adj3 empt* adj3 disorder).tw or dyspep*.tw or eructat*.tw or regurg*.tw

7. fundoplication/ or gastric fundus/ or fundoplic*.tw or (nissen or rossetti or toupet or lind or watson or belsey or dor or hill procedure).tw or (part* adj3 fundoplication).tw or (antireflux adj3 surg*).tw or (antireflux adj3 interven*).tw or (laparosc* adj3 fundoplication).tw or (open adj3 fundoplication).tw or (minim* adj3 fundoplication).tw

8. 5 and 6 and 7

Web of Science search

1. TS=(($esophag* or gastr* or duod*) same (reflux or regurg* or acid or erosion or ulcer)) or TS=(GORD or GERD or heartburn or indigestion or dyspepsia) or TS=($esophagitis or gastritis or gastr* empty* or stomach empty*) or TS=(lower esophag* sphincter or $esophageal motility) or TS=(eructat*) or TS=(hiat* near/3 hernia)

2. TS=(fundoplic* or Nissen or Rossetti or toupet or Watson or belsey or dor or hill procedure) or TS=((antireflux or acid near/3 suppr*) SAME (surg* or laparosc* or open))

3. #1 and #2

C2 Data extraction form

Data Collection Form – Antireflux Network

Trial ID *(name of file or folder; e.g. Mahon 2005)*	
Paper IDs *(if trial's results published in more than one paper; e.g. Grant 2009, Grant 2013b)*	
Publication type *(e.g. full report, abstract, letter)*	Full Report
Possible conflicts of interest *(for study authors)*	
Reviewer	Choo Khoo

Study eligibility

Study Characteristics	Eligibility criteria	Criteria met? Yes	No	Unclear
Type of study	*Randomised Controlled Trial*	○	○	○
	Quasi-randomised Controlled Trial	○	○	○
Participants	*Adult population. GORD based on symptoms **AND** an objective measure (e.g. manometry, endoscopy)*	○	○	○
Intervention	*Fundoplication (open, robotic or lap) for GORD, or other reflux surgical procedure. Exclude procedures specifically for Barrett's, achalasia, extra-oesophageal GORD symptoms.*	○	○	○
Comparison	*Treatment with PPIs, or another surgical procedure. Exclude treatment with other agents (e.g. H2 antagonist)*	○	○	○
Types of outcome measures	*(Health related QOLS; GORD specific QOLS; Dysphagia). (Reflux symptoms; oesophageal acid exposure (score or percentage time); dilatation for dysphagia; reoperation; complications; gas bloating).*	○	○	○
INCLUDE ☐		**EXCLUDE** ☐		
Reason for exclusion				
Notes:				

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of study

Characteristic	Descriptions as stated in report/paper
Other relevant references?	
Unit of allocation *(individuals or cluster)*	Individual
Start and End dates	
Follow-up time points *(if multiple relevant time points reported, record the paper in which each time point was reported e.g. Woodcock 2006 12 months; Nijjar 2010 5 years)*	

Participants

Characteristic	**Description** *(per intervention group where appropriate)*
Study Site(s), Country	
Inclusion criteria	
Exclusion criteria	
Mean or median age	
Gender	Males Females
Severity *(preoperative OGD or pH study)*	
Baseline imbalances	
Total no. randomised	
Total no. analysed	
Withdrawals and exclusions	

Intervention groups

Intervention Group 1 (Surgical Procedure)

Characteristic	Description as stated in report/paper
Group name, no. randomised	
Procedure Details *(for Type: choose from Nissen; Partial posterior; Partial anterior; 90°; mixed; Angelchik; Belsey Mark IV; or other and detail this. For Other: state any peculiarities e.g. rectus abdominis graft/prosthesis)*	**(Type)** Nissen **(Lap/Open/Robotic)** Laparoscopic **(SGV division)** No **(Bougie)** Yes **(Wrap length)** **(Wrap Fixation)** **(Crura Approximated?)** Yes **(Other)**

Intervention Group 2 (Surgical Procedure, or PPI)

Characteristic	Description as stated in report/paper
Group name, no. randomised	
Procedure Details *(for Type: choose from Nissen; Partial posterior; Partial anterior; 90°; mixed; Angelchik; Belsey Mark IV; or other and detail this. For Other: state any peculiarities e.g. rectus abdominis graft/prosthesis. If procedure is PPI, simply state PPI)*	**(Type)** Nissen **(Lap/Open/Robotic)** Laparoscopic **(SGV division)** No **(Bougie)** Yes **(Wrap length)** **(Wrap Fixation)** **(Crura Approximated?)** Yes **(Other)**

Intervention Group 3 (Surgical Procedure, or PPI)

Characteristic	Description as stated in report/paper
Group name, no. randomised	
Procedure Details *(for Type: choose from Nissen; Partial posterior; Partial anterior; 90°; mixed; Angelchik; Belsey Mark IV; or other and detail this. For Other: state any peculiarities e.g. rectus abdominis graft/prosthesis. If procedure is PPI, simply state PPI)*	**(Type)** Nissen **(Lap/Open/Robotic)** Laparoscopic **(SGV division)** No **(Bougie)** Yes **(Wrap length)** **(Wrap Fixation)** **(Crura Approximated?)** Yes **(Other)**

Primary Outcomes (Continuous and Dichotomous)

Outcome*	Unit/Scale**	Time Points	Group 1			Group 2			Group 3		
			N	Mean	SD	N	Mean	SD	N	Mean	SD
Health Related QOLS		3/12 – 1 yr									
		>1yr – 5 yrs									
		>5yrs – 10 yrs									
		>10yrs									
GORD Specific QOLS		3/12 – 1 yr									
		>1yr – 5 yrs									
		>5yrs – 10 yrs									
		>10yrs									
Dysphagia	*(Continuous)*	3/12 – 1 yr									
		>1yr – 5 yrs									
		>5yrs – 10 yrs									
		>10yrs									

			Number with event	Total Number	Number with event	Total Number	Number with event	Total Number
Dysphagia	*(Dichotomous, or scale)*	3/12 – 1 yr						
		>1yr – 5 yrs						
		>5yrs – 10 yrs						
		>10yrs						

* If not enough data reported to enable extraction, state 'Contact with authors required' in 'Unit/Scale' field

** Also state tool used, and if data was calculated or imputed

Secondary Outcomes (Continuous)

Outcome*	Unit/Scale**	Time Points	Group 1			Group 2			Group 3		
			N	Mean	SD	N	Mean	SD	N	Mean	SD
Reflux Symptoms	*(Continuous)*	3/12 – 1 yr									
		>1yr – 5 yrs									
		>5yrs – 10 yrs									
		>10yrs									
Oesophageal acid exposure (De Meester Score)		3/12 – 1 yr									
		>1yr – 5 yrs									
		>5yrs – 10 yrs									
		>10yrs									
Oesophageal acid exposure time (percentage pH<4)		3/12 – 1 yr									
		>1yr – 5 yrs									
		>5yrs – 10 yrs									
		>10yrs									
Gas Bloating	*(Continuous)*	3/12 – 1 yr									
		>1yr – 5 yrs									
		>5yrs – 10 yrs									
		>10yrs									

* If not enough data reported to enable extraction, state 'Contact with authors required' in 'Unit/Scale' field

** Also state tool used, and if data was calculated or imputed

Secondary Outcomes (Dichotomous)

Outcome	Unit/Scale	Time Points	Group 1		Group 2		Group 3	
			Number with event	Total Number	Number with event	Total Number	Number with event	Total Number
Reflux Symptoms	*(Dichotomous, or scale)*	3/12 – 1 yr						
		>1yr – 5 yrs						
		>5yrs – 10 yrs						
		>10yrs						
Dilatation for Dysphagia		3/12 – 1 yr						
		>1yr – 5 yrs						
		>5yrs – 10 yrs						
		>10yrs						
Reoperation Rate		3/12 – 1 yr						
		>1yr – 5 yrs						
		>5yrs – 10 yrs						
		>10yrs						
Gas Bloating	*(Dichotomous, or scale)*	3/12 – 1 yr						
		>1yr – 5 yrs						
		>5yrs – 10 yrs						
		>10yrs						
Postoperative Complications		Any time point >3 months						

* If not enough data reported to enable extraction, state 'Contact with authors required' in 'Unit/Scale' field

** Also state tool used, and if data was calculated or imputed

Risk of Bias assessment

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes where available with explanatory comments)*
Random sequence generation	○ ○ ○	
Allocation concealment	○ ○ ○	
Blinding of patients and personnel	○ ○ ○	
Blinding of outcome assessment	○ ○ ○	
Incomplete outcome data	○ ○ ○	
Selective outcome reporting?	○ ○ ○	
Other bias	○ ○ ○	
Contact with authors required? (missing or incomplete data)		☐

NOTES AND COMMENTS:

APPENDIX D

Bias in surgical trials – additional material

D1 Cochrane Library search

1. (MeSH descriptor general surgery, explode all trees) OR (MeSH descriptor gynecology, explode all trees) OR (MeSH descriptor elective surgical procedures, explode all trees) OR (Mesh descriptor digestive system surgical procedures, explode all trees) OR (MeSH descriptor surgical procedures, operative, explode all trees) OR (MeSH descriptor laparotomy, explode all trees) OR (MeSH descriptor obstetric surgical procedures, explode all trees) OR (open near surgery):ti,ab OR (standard near surgery):ti,ab OR (general surgery) OR (gynecology) OR (operative surgery)

2. (MeSH descriptor minimally invasive surgical procedures, explode all trees) OR (MeSH descriptor ambulatory surgical procedures, explode all trees) OR (MeSH descriptor surgery, computer assisted, explode all trees) OR (laparosc*):ti,ab OR (keyhole):ti,ab OR (minimally invasive)

3. (#1 AND #2)

D2 Data extraction form

Data Collection Form – Risk of Bias

Trial ID *(name of file; e.g. Mahon 2005). Include all file names if same trial published in more than one paper*	
Publication type *(e.g. full report, abstract, letter)*	Full report
Procedure type	Inguinal Hernia
Possible conflicts of interest *(for study authors)*	
Reviewer	Mohammad Amer

Study eligibility

Study Characteristics	Eligibility criteria	Criteria met? Yes	No	Unclear
Type of study	*Randomised Controlled Trial*	○	○	◉
	Quasi-randomised Controlled Trial	○	○	◉
Participants	*Abdominal surgical procedure.*	○	○	◉
Intervention	*Procedure performed laparoscopically*	○	○	◉
Comparison	*Procedure performed open*	○	○	◉
Types of outcome measures	*Length of postoperative stay, postoperative complication rate, pain, time to return of bowel motion/flatus, time to return to normal activities/recovery*	○	○	◉
INCLUDE ◉		**EXCLUDE** ○		
Reason for exclusion				
Notes:				

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Participants

Characteristic	Description *(per intervention group where appropriate)*
Study Site(s), Country	
Key Inclusion/ Exclusion criteria	
Additional References (only if not already included in database)	
Patients	Adults ◉ Paediatric ○ Both ○
Baseline imbalances	
Total no. randomised	
Total no. analysed	
Withdrawals	

Primary Outcomes (Continuous and Dichotomous)

Outcome*	Unit/Scale**	Open			Laparoscopic		
		N	Mean	SD	N	Mean	SD
Length of stay							
		Number with event		Total Number	Number with event		Total Number
Postoperative complication rate							

* If not enough data reported to enable extraction, state 'Contact with authors required' in 'Unit/Scale' field

** Also state tool used, and if data was calculated or imputed

Secondary Outcomes (Continuous)

Outcome*	Unit/Scale**	Open			Laparoscopic		
		N	Mean	SD	N	Mean	SD
Postop pain (<4 weeks)							
(>4 weeks)							
Time to first bowel motion							

Time to first passage of flatus							
Time to recovery							

* If not enough data reported to enable extraction, state 'Contact with authors required' in 'Unit/Scale' field
** Also state tool used, and if data was calculated or imputed

Risk of Bias assessment

Domain	**Risk of bias** **Low High Unclear**	**Support for judgement** *(include direct quotes where available with explanatory comments)*
Random sequence generation	○ ○ ◉	
Allocation concealment	○ ○ ◉	
Blinding – Subjects/Patients *the individuals who are randomly assigned to the intervention under evaluation*	○ ○ ◉	
Blinding – Healthcare providers *the nurses, doctors and other personnel (apart from the operating surgeon) who actually care for the participants during the study period*	○ ○ ◉	
Blinding – Data collectors *the individuals who actually collect data for the study outcomes (e.g. those who administer a questionnaire on postoperative pain)*	○ ○ ◉	
Blinding – Outcome assessors *the individuals who ultimately decide if a participant has suffered/attained the outcome of interest (e.g. return of intestinal function; postoperative complications)*	○ ○ ◉	

Blinding – Data Analysts *the individuals who conduct the data analysis*	○ ○ ◉	
Incomplete outcome data	○ ○ ◉	
Selective outcome reporting?	○ ○ ◉	
Other bias	○ ○ ◉	
Contact with authors required? (further data required for outcomes; or paper reports 'blinded' with no further details) ☐		

NOTES AND COMMENTS:

D3 Included studies

Listed by procedure and trial name in alphabetical order. The name given to each trial (usually surname of first author of first paper, followed by year) is followed by the included publication(s) for that trial.

Appendicectomy

Aktimur 2015

Aktimur, R., Gokakin, A.K., Deveci, K., Atabey, M., and Topcu, O. (2016). Oxidative stress markers in laparoscopic vs. open appendectomy for acute appendicitis: A double-blind randomized study. J Minim Access Surg *12*, 143-147.

Al-Mulhim 2002

Al-Mulhim, A.S., Al-Mulhim, F.M., Al-Suwaiygh, A.A., and Al-Masaud, N.A. (2002). Laparoscopic versus open appendectomy in females with a clinical diagnosis of appendicitis. Saudi Med J *23*, 1339-1342.

Attwood 1992

Attwood, S.E., Hill, A.D., Murphy, P.G., Thornton, J., and Stephens, R.B. (1992). A prospective randomized trial of laparoscopic versus open appendectomy. Surgery *112*, 497-501.

Austin 1992

Austin, O., Hederman, W.P., O'Connell, P.R., Gorey, T.F., and Fitzpatrick, J.M. (1992). Prospective evaluation of laparoscopic versus open appendicectomy. Irish J Med Sci *161*, 92.

Bannon 1997

Long, K.H., Bannon, M.P., Zietlow, S.P., Helgeson, E.R., Harmsen, W.S., Smith, C.D., Ilstrup, D.M., Baerga-Verala, Y., and Sarr, M.G. (2001). A prospective randomized comparison of laparoscopic appendectomy with open appendectomy: clinical and economic analyses. Surgery *129*, 390-400.

Bauwens 1998

Bauwens, K., Schwenk, W., Bohm, B., Hasart, O., Neudecker, J., and Muller, J.M. (1998). [Recovery and duration of work disability after laparoscopic and conventional appendectomy. A prospective randomized study]. Chirurg *69*, 541-545.

Birth 1998

Birth, M., Witten, I., Gadzepko, E., and Weiser, H.F. (1998). Laparoscopic vs open appendectomy for acute appendicitis: a prospective randomized trial. Br J Surg *85 Suppt 2*, 39.

Bliss 2010

Bliss, D., McKee, J., Cho, D., Krishnaswami, S., Zallen, G., Harrison, M., and Silen, M. (2010). Discordance of the pediatric surgeon's intraoperative assessment of pediatric appendicitis with the pathologists report. J Pediatr Surg *45*, 1398-1403.

Bruwer 2003

Bruwer, F., Coetzer, M., and Warren, B.L. (2003). Laparoscopic versus open surgical exploration in premenopausal women with suspected acute appendicitis. S Afr J Surg *41*, 82-85.

Chiarugi 1996

Chiarugi, M., Buccianti, P., Celona, G., Decanini, L., Martino, M.C., Goletti, O., and Cavina, E. (1996). Laparoscopic compared with open appendicectomy for acute appendicitis: a prospective study. Eur J Surg *162*, 385-390.

Cipe 2014

Cipe, G., Idiz, O., Hasbahceci, M., Bozkurt, S., Kadioglu, H., Coskun, H., Karatepe, O., and Muslumanoglu, M. (2014). Laparoscopic versus open appendectomy: where are we now? Chirurgia (Bucur) *109*, 518-522.

Cox 1996

Cox, M.R., McCall, J.L., Toouli, J., Padbury, R.T., Wilson, T.G., Wattchow, D.A., and Langcake, M. (1996). Prospective randomized comparison of open versus laparoscopic appendectomy in men. World J Surg *20*, 263-266.

Eichen 1994

Eichen, R., Heuser, H., and Nitschke, B. (1994). Prospektive studie: laparoskopische appendektomie vs. konventionelle appendektomie. Langenbecks Arch Chir Suppl Kongressbd, 223-225.

Esposito 1997

Esposito, P., Cerbone, D., Rotondano, G., Del Prete, A., Pisano, R., and Cerbone, G. (1997). Laparoscopic appendectomy: our experience. Gastrointest Endosc *45*, AB186.

Frazee 1994

Frazee, R.C., Roberts, J.W., Symmonds, R.E., Snyder, S.K., Hendricks, J.C., Smith, R.W., Custer, M.D., 3rd, and Harrison, J.B. (1994). A prospective randomized trial comparing open versus laparoscopic appendectomy. Ann Surg *219*, 725-728; discussion 728-731.

Hansen 1996

Hansen, J.B., Smithers, B.M., Schache, D., Wall, D.R., Miller, B.J., and Menzies, B.L. (1996). Laparoscopic versus open appendectomy: prospective randomized trial. World J Surg *20*, 17-20; discussion 21.

Hart 1996

Hart, R., Rajgopal, C., Plewes, A., Sweeney, J., Davies, W., Gray, D., and Taylor, B. (1996). Laparoscopic versus open appendectomy: a prospective randomized trial of 81 patients. Can J Surg *39*, 457-462.

Hebebrand 1994

Hebebrand, D., Troidl, H., Spangenberger, W., Neugebauer, E., Schwalm, T., and Gunther, M.W. (1994). [Laparoscopic or classical appendectomy? A prospective randomized study]. Chirurg *65*, 112-120.

Heikkinen 1998

Heikkinen, T.J., Haukipuro, K., and Hulkko, A. (1998). Cost-effective appendectomy: open or laparoscopic? A prospective randomized study. Surg Endosc *12*, 1204-1208.

Hellberg 1999

Hellberg, A., Rudberg, C., Kullman, E., Enochsson, L., Fenyo, G., Graffner, H., Hallerback, B., Johansson, B., Anderberg, B., Wenner, J., *et al.* (1999). Prospective randomized multicentre study of laparoscopic versus open appendicectomy. Br J Surg *86*, 48-53.

Helmy 2001

Helmy, M.A. (2001). A comparative study between laparoscopic versus open appendicectomy in men. J Egypt Soc Parasitol *31*, 555-562.

Henle 1996

Henle, K.P., Beller, S., Rechner, J., Zerz, A., Szinicz, G., and Klingler, A. (1996). [Laparoscopic versus conventional appendectomy: a prospective randomized study]. Chirurg *67*, 526-530; discussion 522.

Klingler, A., Henle, K.P., Beller, S., Rechner, J., Zerz, A., Wetscher, G.J., and Szinicz, G. (1998). Laparoscopic appendectomy does not change the incidence of postoperative infectious complications. Am J Surg *175*, 232-235.

Hoff 1995

Hoff, C., Ruers, T., and Jaklmowicz, J. (1995). Randomized study of laparoscopic versus open appendectomy. Surg Endosc *9*, 605.

Huang 2001

Huang, M.T., Wei, P.L., Wu, C.C., Lai, I.R., Chen, R.J., and Lee, W.J. (2001). Needlescopic, laparoscopic, and open appendectomy: a comparative study. Surg Laparosc Endosc Percutan Tech *11*, 306-312.

Ignacio 2004

Ignacio, R.C., Burke, R., Spencer, D., Bissell, C., Dorsainvil, C., and Lucha, P.A. (2004). Laparoscopic versus open appendectomy: what is the real difference? Results of a prospective randomized double-blinded trial. Surg Endosc *18*, 334-337.

Kald 1999

Kald, A., Kullman, E., Anderberg, B., Wiren, M., Carlsson, P., Ringqvist, I., and Rudberg, C. (1999). Cost-minimisation analysis of laparoscopic and open appendicectomy. Eur J Surg *165*, 579-582.

Kaplan 2009

Kaplan, M., Salman, B., Yilmaz, T.U., and Oguz, M. (2009). A quality of life comparison of laparoscopic and open approaches in acute appendicitis: a randomised prospective study. Acta Chir Belg *109*, 356-363.

Karadayi 2003

Karadayi, K., Turan, M., Canbay, E., Topcu, O., and Sen, M. (2003). Laparoscopic versus open appendectomy: analysis of systemic acute-phase responses in a prospective randomized study. Chirurg Gastroenterol Interdisziplinar *19*, 396-400.

Kathouda 2005

Katkhouda, N., Mason, R.J., Towfigh, S., Gevorgyan, A., and Essani, R. (2005). Laparoscopic versus open appendectomy: a prospective randomized double-blind study. Ann Surg *242*, 439-448; discussion 448-450.

Kazemier 1996

Kazemier, G., de Zeeuw, G.R., Lange, J.F., Hop, W.C., and Bonjer, H.J. (1997). Laparoscopic vs open appendectomy. A randomized clinical trial. Surg Endosc *11*, 336-340.

Kehagias 2009

Kehagias, I., Karamanakos, S., Panagiotopoulos, S., Vagenas, K., and Kalfarentzos, F. (2009). Laparoscopic versus open appendectomy for complicated disease - a prospective randomized trial. Surg Endosc *23*, S13.

Khalil 2011

Khalil, J., Muqim, R., Rafique, M., and Khan, M. (2011). Laparoscopic versus open appendectomy: a comparison of primary outcome measures. Saudi J Gastroenterol *17*, 236-240.

Khan 2014

Khan, I., Khan, M.I., Jawed, M., Shaikh, U., Ahmed, S., and Arif, A. (2014). To compare the frequency of superficial surgical site infection after laparoscopic versus open appendectomy. Med Forum Monthly *25*, 52-55.

Kotlobovsky 2003

Kotlobovsky, V.I., Dronov, A.F., Poddubny, I.V., and Dzhenalaev, B.K. (2003). [Comparative study of surgical and endosurgical treatment of generalized appendicular peritonitis in children]. Khirurgiia *7*, 32-37.

Kouhia 2010

Kouhia, S.T., Heiskanen, J.T., Huttunen, R., Ahtola, H.I., Kiviniemi, V.V., and Hakala, T. (2010). Long-term follow-up of a randomized clinical trial of open versus laparoscopic appendicectomy. Br J Surg *97*, 1395-1400.

Kum 1993

Kum, C.K., Ngoi, S.S., Goh, P.M., Tekant, Y., and Isaac, J.R. (1993). Randomized controlled trial comparing laparoscopic and open appendicectomy. Br J Surg *80*, 1599-1600.

Laine 1997

Laine, S., Rantala, A., Gullichsen, R., and Ovaska, J. (1997). Laparoscopic appendectomy-is it worthwhile? A prospective, randomized study in young women. Surg Endosc *11*, 95-97.

Lavonius 2001

Lavonius, M.I., Liesjarvi, S., Ovaska, J., Pajulo, O., Ristkari, S., and Alanen, M. (2001). Laparoscopic versus open appendectomy in children: a prospective randomised study. Eur J Pediatr Surg *11*, 235-238.

Lejus 1996

Lejus, C., Delile, L., Plattner, V., Baron, M., Guillou, S., Heloury, Y., and Souron, R. (1996). Randomized, single-blinded trial of laparoscopic versus open appendectomy in children: effects on postoperative analgesia. Anesthesiology *84*, 801-806.

Lintula 2001

Lintula, H., Kokki, H., and Vanamo, K. (2001). Single-blind randomized clinical trial of laparoscopic versus open appendicectomy in children. Br J Surg *88*, 510-514.

Lintula, H., Kokki, H., Vanamo, K., Antila, P., and Eskelinen, M. (2002). Laparoscopy in children with complicated appendicitis. J Pediatr Surg *37*, 1317-1320.

Lintula, H., Kokki, H., Vanamo, K., Valtonen, H., Mattila, M., and Eskelinen, M. (2004). The costs and effects of laparoscopic appendectomy in children. Arch Pediatr Adolesc Med *158*, 34-37.

Little 2002

Little, D.C., Custer, M.D., May, B.H., Blalock, S.E., and Cooney, D.R. (2002). Laparoscopic appendectomy: An unnecessary and expensive procedure in children? J Pediatr Surg *37*, 310-317.

Marcarulla 1997

Macarulla, E., Vallet, J., Abad, J.M., Hussein, H., Fernandez, E., and Nieto, B. (1997). Laparoscopic versus open appendectomy: a prospective randomized trial. Surg Laparosc Endosc *7*, 335-339.

Martin 1995

Martin, L.C., Puente, I., Sosa, J.L., Bassin, A., Breslaw, R., McKenney, M.G., Ginzburg, E., and Sleeman, D. (1995). Open versus laparoscopic appendectomy. A prospective randomized comparison. Ann Surg *222*, 256-261; discussion 261-252.

Milewczyk 2003

Milewczyk, M., Michalik, M., and Ciesielski, M. (2003). A prospective, randomized, unicenter study comparing laparoscopic and open treatments of acute appendicitis. Surg Endosc *17*, 1023-1028.

Minne 1997

Minne, L., Varner, D., Burnell, A., Ratzer, E., Clark, J., and Haun, W. (1997). Laparoscopic vs open appendectomy. Prospective randomized study of outcomes. Arch Surg *132*, 708-711; discussion 712.

Moirangthem 2008

Moirangthem, G.S., Arunkumar, C., Marak, A.B., Lokendra, K., and Singh, L.D. (2008). A comparative study between laparoscopic versus open appendicectomy. J Med Soc *22*, 58-62.

Mutter 1996

Mutter, D., Vix, M., Bui, A., Evrard, S., Tassetti, V., Breton, J.F., and Marescaux, J. (1996). Laparoscopy not recommended for routine appendectomy in men: results of a prospective randomized study. Surgery *120*, 71-74.

Navarra 2002

Navarra, G., Ascanelli, S., Turini, A., Carcoforo, P., Tonini, G., and Pozza, E. (2002). [Laparoscopic appendectomy versus open appendectomy in suspected acute appendicitis in female patients]. Ann Ital Chir *73*, 59-63.

Oka 2004

Oka, T., Kurkchubasche, A.G., Bussey, J.G., Wesselhoeft, C.W., Jr., Tracy, T.F., Jr., and Luks, F.I. (2004). Open and laparoscopic appendectomy are equally safe and acceptable in children. Surg Endosc *18*, 242-245.

Olmi 2005

Olmi, S., Magnone, S., Bertolini, A., and Croce, E. (2005). Laparoscopic versus open appendectomy in acute appendicitis: a randomized prospective study. Surg Endosc *19*, 1193-1195.

Ortega 1995

Ortega, A.E., Hunter, J.G., Peters, J.H., Swanstrom, L.L., and Schirmer, B. (1995). A prospective, randomized comparison of laparoscopic appendectomy with open appendectomy. Am J Surg *169*, 208-212; discussion 212-203.

Ozmen 1999

Ozmen, M.M., Zulfikaroglu, B., Tanik, A., and Kale, I.T. (1999). Laparoscopic versus open appendectomy: prospective randomized trial. Surg Laparosc Endosc Percutan Tech *9*, 187-189.

Pedersen 2001

Pedersen, A.G., Petersen, O.B., Wara, P., Ronning, H., Qvist, N., and Laurberg, S. (2001). Randomized clinical trial of laparoscopic versus open appendicectomy. Br J Surg *88*, 200-205.

Pozo 1996

Pozo, J.C., Martinez, S., Negri, C., Rachadell, J.J., and Belloso, R. (1996). [Comparative controled study: laparoscopic vs conventional appendectomies in a teaching program of general surgery]. Revista Soc Venez Gastroenterol *50*, 225-230.

Reiertsen 1997

Reiertsen, O., Larsen, S., Trondsen, E., Edwin, B., Faerden, A.E., and Rosseland, A.R. (1997). Randomized controlled trial with sequential design of laparoscopic versus conventional appendicectomy. Br J Surg *84*, 842-847.

Ricca 2007

Ricca, R., Schneider, J.J., Brar, H., and Lucha, P.A. (2007). Laparoscopic appendectomy in patients with a body mass index of 25 or greater: results of a double blind, prospective, randomized trial. J Soc Laparosc Surg *11*, 54-58.

Rohr 1994

Rohr, S., Thiry, C.L., De Manzini, N., Perrauid, V., and Meyer, C. (1994). Laparoscopic vs open appendectomy in men: a prospective randomized study. Br J Surg *81*, S6-S7.

Sezeur 1997

Sezeur, A., Bure-Rossier, A.M., Rio, D., Savigny, B., Tricot, C., Martel, P., and Baubion, O. (1997). [Does laparoscopy increase the bacteriological risk of appendectomy? Results of a randomized prospective study]. Ann Chir *51*, 243-247.

Shirazi 2010

Shirazi, B., Ali, N., and Shamim, M.S. (2010). Laproscopic versus open appendectomy: a comparative study. J Pak Med Assoc *60*, 901-904.

Simon 2009

Simon, P., Burkhardt, U., Sack, U., Kaisers, U.X., and Muensterer, O.J. (2009). Inflammatory response is no different in children randomized to laparoscopic or open appendectomy. J Laparoendosc Adv Surg Tech A *19 Suppl 1*, S71-76.

Stare 1998

Stare, R., Kocman, I., Povsic Cevra, Z., Zgrebec, Z., and Kovacic, D. (1998). Results of a prospective randomised study of laparoscopic appendectomy in community hospital. Paper presented at: 6th World Congress of Endoscopic Surgery (Rome, Italy: Monduzzi Editore S.p.A., Bologna, Italy (pages 441-445)).

Sun 1998

Sun, X., and Xu, H. (1998). [Comparative study among open, laparoscopic and video-assisted appendectomies]. Huaren Xiaohua Zazhi *6*, 710-711.

Talha 2015

Talha, A.I., and Ghazal, A.H. (2015). Laparoscopic vs open management of perforated appendicitis: A prospective randomized clinical trial. Surg Endosc *29*, S9.

Tate 1993

Tate, J.J., Dawson, J.W., Chung, S.C., Lau, W.Y., and Li, A.K. (1993). Laparoscopic versus open appendicectomy: prospective randomised trial. Lancet *342*, 633-637.

Tzovaras 2007

Tzovaras, G., Baloyiannis, I., Kouritas, V., Symeonidis, D., Spyridakis, M., Poultsidi, A., Tepetes, K., and Zacharoulis, D. (2010). Laparoscopic versus open appendectomy in men: a prospective randomized trial. Surg Endosc *24*, 2987-2992.

Vallribera 2003

Vallribera, F., Sala, J., Aguilar, F., and Espin, E. (2003). [Influence of laparoscopic surgery on perception of quality of life after appendicectomy]. Cir Esp *73*, 88-94.

Wei 2010

Wei, H.B., Huang, J.L., Zheng, Z.H., Wei, B., Zheng, F., Qiu, W.S., Guo, W.P., Chen, T.F., and Wang, T.B. (2010). Laparoscopic versus open appendectomy: a prospective randomized comparison. Surg Endosc *24*, 266-269.

Williams 1996

Williams, M.D., Collins, J.N., Wright, T.F., and Fenoglio, M.E. (1996). Laparoscopic versus open appendectomy. South Med J *89*, 668-674.

Yin 1996

Yin, W.Y., Lee, M.C., Cheng, T.J., Chen, H.T., and Huang, S.M. (1996). Laparoscopic versus open appendectomy: prospective randomized trial. Tzu Chi Med J *8*, 213-221.

Zhang 1998

Zhang, W., Xu, C., and Lin, Y. (1998). [A randomized control study on the appendectomy of 103 cases with laparoscope or mini-incision]. Current Physician *3*, 8-9.

Cholecystectomy

Ahmed 2014

Ahmed, S., Iqbal, T., and Abdullah, M.S. (2014). Open cholecystectomy versus laparoscopic cholecystectomy: A comparative study. Pak J Med Health Sci *8*, 382-385.

Amanollahi 2013

Amanollahi, O., Golpazir, A., and Mansoori, S.A. (2013). [Comparison of complications of open and laparoscopic cholecystectomy in diabetic patients]. Scientific J Kurd Uni Med Sci *18*, 35-40.

Barkun 1992

Barkun, J.S., Barkun, A.N., Sampalis, J.S., Fried, G., Taylor, B., Wexler, M.J., Goresky, C.A., and Meakins, J.L. (1992). Randomised controlled trial of laparoscopic versus mini cholecystectomy. Lancet *340*, 1116-1119.

Bellon 1997

Bellon, J.M., Manzano, L., Bernardos, L., Ga-Honduvilla, N., Larrad, A., Bujan, J., and Alvarez-Mon, M. (1997). Cytokine levels after open and laparoscopic cholecystectomy. Eur Surg Res *29*, 27-34.

Berggren 1994

Berggren, U., Gordh, T., Grama, D., Haglund, U., Rastad, J., and Arvidsson, D. (1994). Laparoscopic versus open cholecystectomy: hospitalization, sick leave, analgesia and trauma responses. Br J Surg *81*, 1362-1365.

Bolke 2000

Bolke, E., Jehle, P.M., Nothnagel, B., Seidelmann, M., Storck, M., and Orth, K. (2000). A prospective randomised study on endotoxaemia, mediator release and morbidity in conventional, compared with laparoscopic cholecystectomy. Min Inv Ther Allied Tech *9*, 387-392.

Boo 2007

Boo, Y.J., Kim, W.B., Kim, J., Song, T.J., Choi, S.Y., Kim, Y.C., and Suh, S.O. (2007). Systemic immune response after open versus laparoscopic cholecystectomy in acute cholecystitis: a prospective randomized study. Scand J Clin Lab Inv *67*, 207-214.

Bukan 2004

Bukan, M.H., Bukan, N., Kaymakcioglu, N., and Tufan, T. (2004). Effects of open vs. laparoscopic cholecystectomy on oxidative stress. Tohoku J Exp Med *202*, 51-56.

Catena 2008

Catena, F., Ansaloni, L., Bianchi, E., Di Saverio, S., Coccolini, F., Vallicelli, C., Lazzareschi, D., Sartelli, M., Amaduzzi, A., Amaduzz, A., *et al.* (2013). The ACTIVE (Acute Cholecystitis Trial Invasive Versus Endoscopic) study: multicenter randomized, double-blind, controlled trial of laparoscopic versus open surgery for acute cholecystitis. Hepato-gastroenterol *60*, 1552-1556.

Charlo 1995

Charlo Dupont, T., Fernandez Martin, M., and Tejido Sanchez, C. (1995). [Cost analysis of laparoscopic cholecystectomy compared to open]. Rev Esp Enf Digest *87*, 449-452.

Chumillas 1998

Chumillas, M.S., Ponce, J.L., Delgado, F., and Viciano, V. (1998). Pulmonary function and complications after laparoscopic cholecystectomy. Eur J Surg *164*, 433-437.

Coelho 1993

Coelho, J.C., de Araujo, R.P., Marchesini, J.B., Coelho, I.C., and de Araujo, L.R. (1993). Pulmonary function after cholecystectomy performed through Kocher's incision, a mini-incision, and laparoscopy. World J Surg *17*, 544-546.

Dauleh 1995

Dauleh, M.I., Rahman, S., and Townell, N.H. (1995). Open versus laparoscopic cholecystectomy: a comparison of postoperative temperature. J R Coll Surg Edinb *40*, 116-118.

Demirer 2000

Demirer, S., Karadayi, K., Simsek, S., Erverdi, N., and Bumin, C. (2000). Comparison of postoperative acute-phase reactants in patients who underwent laparoscopic v open cholecystectomy: a randomized study. J Laparoendosc Adv Surg Tech A *10*, 249-252.

Dionigi 1994

Dionigi, R., Dominioni, L., Benevento, A., Giudice, G., Cuffari, S., Bordone, N., Caravati, F., Carcano, G., and Gennari, R. (1994). Effects of surgical trauma of laparoscopic vs. open cholecystectomy. Hepato-gastroenterol *41*, 471-476.

El-Awadi 2009

El-Awadi, S., El-Nakeeb, A., Youssef, T., Fikry, A., Abd El-Hamed, T.M., Ghazy, H., Foda, E., and Farid, M. (2009). Laparoscopic versus open cholecystectomy in cirrhotic patients: a prospective randomized study. Int J Surg *7*, 66-69.

Galizia 2001

Galizia, G., Prizio, G., Lieto, E., Castellano, P., Pelosio, L., Imperatore, V., Ferrara, A., and Pignatelli, C. (2001). Hemodynamic and pulmonary changes during open, carbon dioxide pneumoperitoneum and abdominal wall-lifting cholecystectomy. A prospective, randomized study. Surg Endosc *15*, 477-483.

Garcia-Caballero 1993

Garcia-Caballero, M., and Vara-Thorbeck, C. (1993). The evolution of postoperative ileus after laparoscopic cholecystectomy. A comparative study with conventional cholecystectomy and sympathetic blockade treatment. Surg Endosc *7*, 416-419.

Grande 2002

Grande, M., Tucci, G.F., Adorisio, O., Barini, A., Rulli, F., Neri, A., Franchi, F., and Farinon, A.M. (2002). Systemic acute-phase response after laparoscopic and open cholecystectomy. Surg Endosc *16*, 313-316.

Hamad 2010

Hamad, M.A., Thabet, M., Badawy, A., Mourad, F., Abdel-Salam, M., Abdel-Rahman M.E., Hafez, M.Z., and Sherif, T. (2010). Laparoscopic versus open cholecystectomy in patients with liver cirrhosis: a prospective, randomized study. J Laparoendosc Adv Surg Tech A *20*, 405-409.

Harju 2006

Harju, J., Juvonen, P., Eskelinen, M., Miettinen, P., and Paakkonen, M. (2006). Minilaparotomy cholecystectomy versus laparoscopic cholecystectomy: a randomized study with special reference to obesity. Surg Endosc *20*, 583-586.

Harju, J., Paakkonen, M., and Eskelinen, M. (2007). Comparison of the quality of life after minilaparotomy cholecystectomy versus laparoscopic cholecystectomy: a prospective randomized study. Israel Med Assoc J *9*, 147-148.

Harju 2010

Harju, J., Kokki, H., Paakkonen, M., Karjalainen, K., and Eskelinen, M. (2010). Feasibility of minilaparotomy versus laparoscopic cholecystectomy for day surgery: a prospective randomised study. Scand J Surg *99*, 132-136.

Harju 2013

Harju, J., Juvonen, P., Kokki, H., Remes, V., Scheinin, T., and Eskelinen, M. (2013). Minilaparotomy cholecystectomy with ultrasonic dissection versus conventional laparoscopic cholecystectomy: a randomized multicenter study. Scan J Gastroenterol *48*, 1317-1323.

Hendolin 2000

Hendolin, H.I., Paakonen, M.E., Alhava, E.M., Tarvainen, R., Kemppinen, T., and Lahtinen, P. (2000). Laparoscopic or open cholecystectomy: a prospective randomised trial to compare postoperative pain, pulmonary function, and stress response. Eur J Surg *166*, 394-399.

Huang 1996

Huang, S.M., Wu, C.W., Lui, W.Y., and P'Eng F, K. (1996). A prospective randomised study of laparoscopic v. open cholecystectomy in aged patients with cholecystolithiasis. S Afr J Surg *34*, 177-179; discussion 179-180.

Jan 1993

Jan, Y.Y., and Chen, M.F. (1993). [Laparoscopic versus open cholecystectomy: a prospective randomized study]. J Formos Med Assoc *92*, S243-249.

Ji 2005

Ji, W., Li, L.-T., Wang, Z.-M., Quan, Z.-F., Chen, X.-R., and Li, J.-S. (2005). A randomized controlled trial of laparoscopic versus open cholecystectomy in patients with cirrhotic portal hypertension. World J of Gastroenterol *11*, 2513-2517.

Johansson 2005

Johansson, M., Thune, A., Nelvin, L., Stiernstam, M., Westman, B., and Lundell, L. (2005). Randomized clinical trial of open versus laparoscopic cholecystectomy in the treatment of acute cholecystitis. BJS *92*, 44-49.

Karayiannakis 1997

Karayiannakis, A.J., Makri, G.G., Mantzioka, A., Karousos, D., and Karatzas, G. (1996). Postoperative pulmonary function after laparoscopic and open cholecystectomy. Br J Anaesth *77*, 448-452.

Karayiannakis, A.J., Makri, G.G., Mantzioka, A., Karousos, D., and Karatzas, G. (1997). Systemic stress response after laparoscopic or open cholecystectomy: a randomized trial. Br J Surg *84*, 467-471.

Keus 2007

Keus, F., Ahmed Ali, U., Noordergraaf, G.J., Roukema, J.A., Gooszen, H.G., and van Laarhoven, C.J.H.M. (2007). Anaesthesiological considerations in small-incision and laparoscopic cholecystectomy in symptomatic cholecystolithiasis: implications for pulmonary function. A randomized clinical trial. Acta Anaesthesiol Scand *51*, 1068-1078.

Keus, F., Werner, J.E.M., Gooszen, H.G., Oostvogel, H.J.M., and van Laarhoven, C.J.H.M. (2008). Randomized clinical trial of small-incision and laparoscopic cholecystectomy in patients with symptomatic cholecystolithiasis: primary and clinical outcomes. Arch Surg *143*, 371-378.

Khan 2014

Khan, M.A., Naeem, M., Manan, F., Abdullah, Haleem, A., Ahmad, I., and Alam, Q. (2014). Laparoscopic versus mini-cholecystectomy. J Med Sci *22*, 9-12.

Kiviluoto 1998

Kiviluoto, T., Siren, J., Luukkonen, P., and Kivilaakso, E. (1998). Randomised trial of laparoscopic versus open cholecystectomy for acute and gangrenous cholecystitis. Lancet *351*, 321-325.

Kunz 1992

Kunz, R., Orth, K., Vogel, J., Steinacker, J.M., Meitinger, A., Bruckner, U., and Beger, H.G. (1992). [Laparoscopic cholecystectomy versus mini-lap-cholecystectomy. Results of a prospective, randomized study]. Chirurg *63*, 291-295.

Lausten 1999

Lausten, S.B., Ibrahim, T.M., El-Sefi, T., Jensen, L.S., Gesser, B., Larsen, C.G., Tonnesen, E., and Jensen, S.L. (1999). Systemic and cell-mediated immune response after laparoscopic and open cholecystectomy in patients with chronic liver disease. A randomized, prospective study. Dig Surg *16*, 471-477.

Le Blanc-Louvry 2000

Le Blanc-Louvry, I., Coquerel, A., Koning, E., Maillot, C., and Ducrotte, P. (2000). Operative stress response is reduced after laparoscopic compared to open cholecystectomy: the relationship with postoperative pain and ileus. Dig Dis Sci *45*, 1703-1713.

Lujan 1998

Lujan, J.A., Sanchez-Bueno, F., Parrilla, P., Robles, R., Torralba, J.A., and Gonzalez-Costea, R. (1998). Laparoscopic vs. open cholecystectomy in patients aged 65 and older. Surg Laparosc Endosc *8*, 208-210.

Luo 2003

Luo, K., Li, J.S., Li, L.T., Wang, K.H., and Shun, J.M. (2003). Operative stress response and energy metabolism after laparoscopic cholecystectomy compared to open surgery. World J Gastroenterol *9*, 847-850.

Majeed 1996

Majeed, A.W., Troy, G., Nicholl, J.P., Smythe, A., Reed, M.W., Stoddard, C.J., Peacock, J., and Johnson, A.G. (1996). Randomised, prospective, single-blind comparison of laparoscopic versus small-incision cholecystectomy. Lancet *347*, 989-994.

Squirrell, D.M., Majeed, A.W., Troy, G., Peacock, J.E., Nicholl, J.P., and Johnson, A.G. (1998). A randomized, prospective, blinded comparison of postoperative pain, metabolic response, and perceived health after laparoscopic and small incision cholecystectomy. Surgery *123*, 485-495.

McGinn 1995

McGinn, F.P., Miles, A.J., Uglow, M., Ozmen, M., Terzi, C., and Humby, M. (1995). Randomized trial of laparoscopic cholecystectomy and mini-cholecystectomy. Br J Surg *82*, 1374-1377.

McMahon 1993

McMahon, A.J., Russell, I.T., Baxter, J.N., Ross, S., Anderson, J.R., Morran, C.G., Sunderland, G., Galloway, D., Ramsay, G., and O'Dwyer, P.J. (1994). Laparoscopic versus minilaparotomy cholecystectomy: a randomised trial. Lancet *343*, 135-138.

McMahon, A.J., Ross, S., Baxter, J.N., Russell, I.T., Anderson, J.R., Morran, C.G., Sunderland, G.T., Galloway, D.J., and O'Dwyer, P.J. (1995). Symptomatic outcome 1 year after laparoscopic and minilaparotomy cholecystectomy: a randomized trial. Br J Surg *82*, 1378-1382.

Mimica 2000

Mimica, Z., Biocic, M., Bacic, A., Banovic, I., Tocilj, J., Radonic, V., Ilic, N., and Petricevic, A. (2000). Laparoscopic and laparotomic cholecystectomy: a randomized trial comparing postoperative respiratory function. Respiration *67*, 153-158.

Morshed 2003

Morshed, M., El-Awadi, S., Khafagi, W., Moatamed, A., and Ragab, E. (2003). A comparison of laparoscopic and open cholecystectomy in patients with compensated cirrhosis and symptomatic gall stones. Egypt J Surg *22*, 249-255.

Ortega 1996

Ortega, A.E., Peters, J.H., Incarbone, R., Estrada, L., Ehsan, A., Kwan, Y., Spencer, C.J., Moore-Jeffries, E., Kuchta, K., and Nicoloff, J.T. (1996). A prospective randomized comparison of the metabolic and stress hormonal responses of laparoscopic and open cholecystectomy. J Am Coll Surg *183*, 249-256.

Putensen-Himmer 1992

Putensen-Himmer, G., Putensen, C., Lammer, H., Lingnau, W., Aigner, F., and Benzer, H. (1992). Comparison of postoperative respiratory function after laparoscopy or open laparotomy for cholecystectomy. Anesthesiology *77*, 675-680.

Redmond 1994

Redmond, H.P., Watson, R.W., Houghton, T., Condron, C., Watson, R.G., and Bouchier-Hayes, D. (1994). Immune function in patients undergoing open vs laparoscopic cholecystectomy. Arch Surg *129*, 1240-1246.

Ros 2001

Ros, A., Gustafsson, L., Krook, H., Nordgren, C.E., Thorell, A., Wallin, G., and Nilsson, E. (2001). Laparoscopic cholecystectomy versus mini-laparotomy cholecystectomy: a prospective, randomized, single-blind study. Ann Surg *234*, 741-749.

Saeed 2007

Saeed, T., Zarin, M., Aurangzeb, M., Wazir, A., and Muqeem, R. (2007). Comparative study of laparoscopic versus open cholecysyectomy. Pak J Surg *23*, 96-99.

Schauer 1993

Schauer, P.R., Luna, J., Ghiatas, A.A., Glen, M.E., Warren, J.M., and Sirinek, K.R. (1993). Pulmonary function after laparoscopic cholecystectomy. Surgery *114*, 389-397; discussion 397-389.

Secco 2002

Secco, G.B., Cataletti, M., Bonfante, P., Baldi, E., Davini, M.D., Biasotti, B., Ravera, G., and Ferraris, R. (2002). [Laparoscopic versus mini-cholecystectomy: analysis of hospital costs and social costs in a prospective randomized study]. Chirurg Ital *54*, 685-692.

Siddiqui 2006

Siddiqui, K., and Khan, A.F. (2006). Comparison of frequency of wound infection: open vs laparoscopic cholecystectomy. J Ayub Med Coll *18*, 21-24.

Srivastava 2001

Srivastava, A., Srinivas, G., Misra, M.C., Pandav, C.S., Seenu, V., and Goyal, A. (2001). Cost-effectiveness analysis of laparoscopic versus minilaparotomy cholecystectomy for gallstone disease. A randomized trial. Int J Technol Assess Health Care *17*, 497-502.

Tate 1993

Tate, J.J., Dawson, J.W., Chung, S.C., Lau, W.Y., and Li, A.K. (1993). Laparoscopic versus open appendicectomy: prospective randomised trial. Lancet *342*, 633-637.

Trondsen 1993

Trondsen, E., Reiertsen, O., Andersen, O.K., and Kjaersgaard, P. (1993). Laparoscopic and open cholecystectomy. A prospective, randomized study. Eur J Surg *159*, 217-221.

Kjaersgaard, P., Reiertsen, O., Trondsen, E., Rosseland, A.R., and Larsen, S. (1994). Comparison of sequential and fixed-sample designs in a controlled clinical trial with laparoscopic versus conventional cholecystectomy. Scand J Gastroenterol *29*, 854-858.

Vagenas 2006

Vagenas, K., Spyrakopoulos, P., Karanikolas, M., Sakelaropoulos, G., Maroulis, I., and Karavias, D. (2006). Mini-laparotomy cholecystectomy versus laparoscopic cholecystectomy: which way to go? Surg Laparosc Endosc Percutan Tech *16*, 321-324.

Velazquez-Mendoza 2012

Velazquez-Mendoza, J.D., Villagran-Murillo, F.J., and Gonzalez-Ojeda, A. (2012). Minilaparotomy vs. laparoscopic cholecystectomy: results of a randomized clinical trial. Cir Cirujanos *80*, 115-121.

Volpino 1998

Volpino, P., Cangemi, V., D'Andrea, N., Cangemi, B., and Piat, G. (1998). Hemodynamic and pulmonary changes during and after laparoscopic cholecystectomy. A comparison with traditional surgery. Surg Endosc *12*, 119-123.

Walker 1999

Walker, C.B., Bruce, D.M., Heys, S.D., Gough, D.B., Binnie, N.R., and Eremin, O. (1999). Minimal modulation of lymphocyte and natural killer cell subsets following minimal access surgery. Am J Surg *177*, 48-54.

Zajac 1998

Zajac, M., Zajac, K., and Engel, Z. (1998). Laparoscopy vs laparotomy for cholecystectomy in elderly patients [abstract]. Br J Anaesth *80*, 2.

Colonic Resection

ALCCaS

Hewett, P.J., Allardyce, R.A., Bagshaw, P.F., Frampton, C.M., Frizelle, F.A., Rieger, N.A., Smith, J.S., Solomon, M.J., Stephens, J.H., and Stevenson, A.R. (2008). Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. Ann Surg *248*, 728-738.

Allardyce, R.A., Bagshaw, P.F., Frampton, C.M., Frizelle, F.A., Hewett, P.J., Rieger, N.A., Smith, J.S., Solomon, M.J., Stevenson, A.R., and Australasian Laparoscopic Colon Cancer Study, G. (2010). Australasian Laparoscopic Colon Cancer Study shows that elderly patients may benefit from lower postoperative complication rates following laparoscopic versus open resection. Br J Surg *97*, 86-91.

Basse 2005

Basse, L., Jakobsen, D.H., Bardram, L., Billesbolle, P., Lund, C., Mogensen, T., Rosenberg, J., and Kehlet, H. (2005). Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. Ann Surg *241*, 416-423.

Braga 2002a

Braga, M., Vignali, A., Gianotti, L., Zuliani, W., Radaelli, G., Gruarin, P., Dellabona, P., and Di Carlo, V. (2002). Laparoscopic versus open colorectal surgery: a randomized trial on short-term outcome. Ann Surg *236*, 759-766; disscussion 767.

Frasson, M., Braga, M., Vignali, A., Zuliani, W., and Di Carlo, V. (2008). Benefits of laparoscopic colorectal resection are more pronounced in elderly patients. Dis Colon Rectum *51*, 296-300.

Braga 2002b

Braga, M., Vignali, A., Zuliani, W., Radaelli, G., Gianotti, L., Martani, C., Toussoun, G., and Di Carlo, V. (2002). Metabolic and functional results after laparoscopic colorectal surgery: a randomized, controlled trial. Dis Colon Rectum *45*, 1070-1077.

Braga 2010

Braga, M., Frasson, M., Zuliani, W., Vignali, A., Pecorelli, N., and Di Carlo, V. (2010). Randomized clinical trial of laparoscopic versus open left colonic resection. Br J Surg *97*, 1180-1186.

Carli 2005

Carli, F., Galeone, M., Gzodzic, B., Hong, X., Fried, G.M., Wykes, L., Eberhart, L., and Schricker, T. (2005). Effect of laparoscopic colon resection on postoperative glucose utilization and protein sparing: an integrated analysis of glucose and protein metabolism during the fasted and fed States using stable isotopes. Arch Surg *140*, 593-597.

Chung 2007

Chung, C.C., Ng, D.C., Tsang, W.W., Tang, W.L., Yau, K.K., Cheung, H.Y., Wong, J.C., and Li, M.K. (2007). Hand-assisted laparoscopic versus open right colectomy: a randomized controlled trial. Ann Surg *246*, 728-733.

COLOR

Veldkamp, R., Kuhry, E., Hop, W.C., Jeekel, J., Kazemier, G., Bonjer, H.J., Haglind, E., Pahlman, L., Cuesta, M.A., Msika, S., *et al.* (2005). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol *6*, 477-484.

Janson, M., Lindholm, E., Anderberg, B., and Haglind, E. (2007). Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer. Surg Endosc *21*, 747-753.

COST

Weeks, J.C., Nelson, H., Gelber, S., Sargent, D., Schroeder, G., and Clinical Outcomes of Surgical Therapy Study, G. (2002). Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. JAMA *287*, 321-328.

Clinical Outcomes of Surgical Therapy Study, G., Nelson, H., Sargent, D.J., Wieand, H.S., Fleshman, J., Anvari, M., Stryker, S.J., Beart, R.W., Jr., Hellinger, M., Flanagan, R., Jr., *et al.* (2004). A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med *350*, 2050-2059.

Curet 2000

Curet, M.J., Putrakul, K., Pitcher, D.E., Josloff, R.K., and Zucker, K.A. (2000). Laparoscopically assisted colon resection for colon carcinoma: perioperative results and long-term outcome. Surg Endosc *14*, 1062-1066.

Danelli 2002

Danelli, G., Berti, M., Perotti, V., Albertin, A., Baccari, P., Deni, F., Fanelli, G., and Casati, A. (2002). Temperature control and recovery of bowel function after laparoscopic or laparotomic colorectal surgery in patients receiving combined epidural/general anesthesia and postoperative epidural analgesia. Anesth Analg *95*, 467-47.

EnROL

Kennedy, R.H., Francis, E.A., Wharton, R., Blazeby, J.M., Quirke, P., West, N.P., and Dutton, S.J. (2014). Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol *32*, 1804-1811.

Fujii 2013

Fujii, S., Ishibe, A., Ota, M., Yamagishi, S., Watanabe, K., Watanabe, J., Kanazawa, A., Ichikawa, Y., Oba, M., Morita, S., *et al.* (2014). Short-term results of a randomized study between laparoscopic and open surgery in elderly colorectal cancer patients. Surg Endosc *28*, 466-476.

Gervaz 2010

Gervaz, P., Inan, I., Perneger, T., Schiffer, E., and Morel, P. (2010). A prospective, randomized, single-blind comparison of laparoscopic versus open sigmoid colectomy for diverticulitis. Ann Surg *252*, 3-8.

Gong 2012

Gong, J., Shi, D.B., Li, X.X., Cai, S.J., Guan, Z.Q., and Xu, Y. (2012). Short-term outcomes of laparoscopic total mesorectal excision compared to open surgery. World J Gastroenterol *18*, 7308-7313.

Hasegawa 2003

Hasegawa, H., Kabeshima, Y., Watanabe, M., Yamamoto, S., and Kitajima, M. (2003). Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. Surg Endosc *17*, 636-640.

Hewitt 1998

Hewitt, P.M., Ip, S.M., Kwok, S.P., Somers, S.S., Li, K., Leung, K.L., Lau, W.Y., and Li, A.K. (1998). Laparoscopic-assisted vs. open surgery for colorectal cancer: comparative study of immune effects. Dis Colon Rectum *41*, 901-909.

JCOG 0404

Yamamoto, S., Inomata, M., Katayama, H., Mizusawa, J., Etoh, T., Konishi, F., Sugihara, K., Watanabe, M., Moriya, Y., Kitano, S., *et al.* (2014). Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. Ann Surg *260*, 23-30.

Kaiser 2004

Kaiser, A.M., Kang, J.C., Chan, L.S., Vukasin, P., and Beart, R.W., Jr. (2004). Laparoscopic-assisted vs. open colectomy for colon cancer: a prospective randomized trial. J Laparoendosc Adv Surg Tech A *14*, 329-334.

Kang 2004

Kang, J.C., Chung, M.H., Chao, P.C., Yeh, C.C., Hsiao, C.W., Lee, T.Y., and Jao, S.W. (2004). Hand-assisted laparoscopic colectomy vs open colectomy: a prospective randomized study. Surg Endosc *18*, 577-581.

King 2006

King, P.M., Blazeby, J.M., Ewings, P., Franks, P.J., Longman, R.J., Kendrick, A.H., Kipling, R.M., and Kennedy, R.H. (2006). Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. BJS *93*, 300-308.

Lacy 1995

Lacy, A.M., Garcia-Valdecasas, J.C., Pique, J.M., Delgado, S., Campo, E., Bordas, J.M., Taura, P., Grande, L., Fuster, J., Pacheco, J.L., *et al.* (1995). Short-term outcome analysis of a randomized study comparing laparoscopic vs open colectomy for colon cancer. Surg Endosc *9*, 1101-1105.

Lacy, A.M., Garcia-Valdecasas, J.C., Delgado, S., Castells, A., Taura, P., Pique, J.M., and Visa, J. (2002). Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet *359*, 2224-2229.

LAFA

Vlug, M.S., Wind, J., Hollmann, M.W., Ubbink, D.T., Cense, H.A., Engel, A.F., Gerhards, M.F., van Wagensveld, B.A., van der Zaag, E.S., van Geloven, A.A., *et al.* (2011). Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg *254*, 868-875.

Li 2012

Li, J.C., Leung, K.L., Ng, S.S., Liu, S.Y., Lee, J.F., and Hon, S.S. (2012). Laparoscopic-assisted versus open resection of right-sided colonic cancer - a prospective randomized controlled trial. Int J Colorectal Dis *27*, 95-102.

Liang 2002

Liang, J.T., Shieh, M.J., Chen, C.N., Cheng, Y.M., Chang, K.J., and Wang, S.M. (2002). Prospective evaluation of laparoscopy-assisted colectomy versus laparotomy with resection for management of complex polyps of the sigmoid colon. World J Surg *26*, 377-383.

Liang 2007

Liang, J.T., Huang, K.C., Lai, H.S., Lee, P.H., and Jeng, Y.M. (2007). Oncologic results of laparoscopic versus conventional open surgery for stage II or III left-*sided* colon cancers: a randomized controlled trial. Ann Surg Oncol *14*, 109-117.

Liu 2007

Liu, F.L., Ye, F., Lin, J.J., Xu, X.M., and Xu, J.H. (2007). [Clinical study of hand-assisted laparoscopic total colectomy for colonic inertia]. Zhonghua Wai Ke Za Zhi *45*, 1305-1307.

Maartense 2006

Maartense, S., Dunker, M.S., Slors, J.F., Cuesta, M.A., Pierik, E.G., Gouma, D.J., Hommes, D.W., Sprangers, M.A., and Bemelman, W.A. (2006). Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. Ann Surg *243*, 143-149; discussion 150-143.

Milsom 1998

Milsom, J.W., Bohm, B., Hammerhofer, K.A., Fazio, V., Steiger, E., and Elson, P. (1998). A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. J Am Coll Surg *187*, 46-54; discussion 54-45.

Milsom 2001

Milsom, J.W., Hammerhofer, K.A., Bohm, B., Marcello, P., Elson, P., and Fazio, V.W. (2001). Prospective, randomized trial comparing laparoscopic vs. conventional surgery for refractory ileocolic Crohn's disease. Dis Colon Rectum *44*, 1-8; discussion 8-9.

MRC CLASSIC

Guillou, P.J., Quirke, P., Thorpe, H., Walker, J., Jayne, D.G., Smith, A.M., Heath, R.M., Brown, J.M., and group, M.C.t. (2005). Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet *365*, 1718-1726.

Neudecker 2002

Neudecker, J., Junghans, T., Ziemer, S., Raue, W., and Schwenk, W. (2002). Effect of laparoscopic and conventional colorectal resection on peritoneal fibrinolytic capacity: a prospective randomized clinical trial. Int J Colorectal Dis *17*, 426-429.

Neudecker 2009

Neudecker, J., Klein, F., Bittner, R., Carus, T., Stroux, A., Schwenk, W., and Trialists, L.I. (2009). Short-term outcomes from a prospective randomized trial comparing laparoscopic and open surgery for colorectal cancer. Br J Surg *96*, 1458-1467.

Ordemann 2001

Ordemann, J., Jacobi, C.A., Schwenk, W., Stosslein, R., and Muller, J.M. (2001). Cellular and humoral inflammatory response after laparoscopic and conventional colorectal resections. Surg Endosc *15*, 600-608.

Ortiz 1996

Ortiz, H., Armendariz, P., and Yarnoz, C. (1996). Early postoperative feeding after elective colorectal surgery is not a benefit unique to laparoscopy-assisted procedures. Int J Colorectal Dis *11*, 246-249.

Pappas-Gogos 2013

Pappas-Gogos, G., Tellis, C., Lasithiotakis, K., Tselepis, A.D., Tsimogiannis, K., Tsimoyiannis, E., Chalkiadakis, G., and Chrysos, E. (2013). Oxidative stress markers in laparoscopic versus open colectomy for cancer: a double-blind randomized study. Surg Endosc *27*, 2357-2365.

Pascual 2011

Pascual, M., Alonso, S., Pares, D., Courtier, R., Gil, M.J., Grande, L., and Pera, M. (2011). Randomized clinical trial comparing inflammatory and angiogenic response after open versus laparoscopic curative resection for colonic cancer. Br J Surg *98*, 50-59.

Ramacciato 2008

Ramacciato, G., D'Angelo, F., Aurello, P., Nigri, G., Valabrega, S., Pezzoli, F., Ravaioli, M., Cescon, M., Cucchetti, A., Lauro, A., *et al.* (2008). [Right hemicolectomy for colon cancer: a prospective randomised study comparing laparoscopic vs. open technique]. Chir Ital *60*, 1-7.

Raue 2011

Raue, W., Paolucci, V., Asperger, W., Albrecht, R., Buchler, M.W., Schwenk, W., and Group, L.-C.T. (2011). Laparoscopic sigmoid resection for diverticular disease has no advantages over open approach: midterm results of a randomized controlled trial. Langenbecks Arch Surg *396*, 973-980.

Schietroma 2013

Schietroma, M., Pessia, B., Carlei, F., Cecilia, E.M., De Santis, G., and Amicucci, G. (2015). Laparoscopic versus open colorectal surgery for colon cancer: the effect of surgical trauma on the bacterial translocation. A prospective randomized study. Am J Surg *210*, 263-269.

Schwenk 1998

Schwenk, W., Bohm, B., and Muller, J.M. (1998). Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. A prospective randomized trial. Surg Endosc *12*, 1131-1136.

Schwenk, W., Bohm, B., Haase, O., Junghans, T., and Muller, J.M. (1998). Laparoscopic versus conventional colorectal resection: a prospective randomised study of postoperative ileus and early postoperative feeding. Langenbecks Arch Surg *383*, 49-55.

Schwenk, W., Bohm, B., Witt, C., Junghans, T., Grundel, K., and Muller, J.M. (1999). Pulmonary function following laparoscopic or conventional colorectal resection: a randomized controlled evaluation. Arch Surg *134*, 6-12; discussion 13.

Sigma

Klarenbeek, B.R., Peet, D.L., and Cuesta, M.A. (2009). Laparoscopic sigmoid resection for diverticulitis decreases major morbidity rates: A randomized controlled trial. Ann Surg *250*, 501-502.

Stage 1997

Stage, J.G., Schulze, S., Moller, P., Overgaard, H., Andersen, M., Rebsdorf-Pedersen, V.B., and Nielsen, H.J. (1997). Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. Br J Surg *84*, 391-396.

Tang 2001

Tang, C.L., Eu, K.W., Tai, B.C., Soh, J.G., MacHin, D., and Seow-Choen, F. (2001). Randomized clinical trial of the effect of open versus laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer. Br J Surg *88*, 801-807.

Tung 2013

Cheung, H.Y., Chung, C.C., Tsang, W.W., Wong, J.C., Yau, K.K., and Li, M.K. (2009). Endolaparoscopic approach vs conventional open surgery in the treatment of obstructing left-sided colon cancer: a randomized controlled trial. Arch Surg *144*, 1127-1132.

Xu 2012

Xu, L.-S., and Liu, W.-S. (2012). A prospective, randomized, single-blind comparison of laparoscopic versus open colectomy for slow-transit constipation. American Surgeon *78*, 495-496.

Donor Nephrectomy

Basiri 2007

Basiri, A., Simforoosh, N., Heidari, M., Moghaddam, S.M., and Otookesh, H. (2007). Laparoscopic v open donor nephrectomy for pediatric kidney recipients: preliminary report of a randomized controlled trial. J Endourol *21*, 1033-1036.

Burgess 2007

Burgess, N.A., Koo, B.C., Calvert, R.C., Hindmarsh, A., Donaldson, P.J., and Rhodes, M. (2007). Randomized trial of laparoscopic v open nephrectomy. J Endourol *21*, 610-613.

Guleria 2008

Guleria, S. (2010). Mini-donor nephrectomy: a viable and effective alternative. Indian J Urol *26*, 139-141.

Kok 2006

Kok, N.F., Lind, M.Y., Hansson, B.M., Pilzecker, D., Mertens zur Borg, I.R., Knipscheer, B.C., Hazebroek, E.J., Dooper, I.M., Weimar, W., Hop, W.C., *et al.* (2006). Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ *333*, 221.

Kok, N.F., Adang, E.M., Hansson, B.M., Dooper, I.M., Weimar, W., van der Wilt, G.J., and Ijzermans, J.N. (2007). Cost effectiveness of laparoscopic versus mini-incision open donor nephrectomy: a randomized study. Transplantation *83*, 1582-1587.

Dols, L.F., Ijzermans, J.N., Wentink, N., Tran, T.C., Zuidema, W.C., Dooper, I.M., Weimar, W., and Kok, N.F. (2010). Long-term follow-up of a randomized trial comparing laparoscopic and mini-incision open live donor nephrectomy. Am J Transplant *10*, 2481-2487.

Nicholson 2010

Nicholson, M.L., Kaushik, M., Lewis, G.R., Brook, N.R., Bagul, A., Kay, M.D., Harper, S.J., Elwell, R., and Veitch, P.S. (2010). Randomized clinical trial of laparoscopic versus open donor nephrectomy. Br J Surg *97*, 21-28.

Nicholson, M.L., Elwell, R., Kaushik, M., Bagul, A., and Hosgood, S.A. (2011). Health-related quality of life after living donor nephrectomy: a randomized controlled trial of laparoscopic versus open nephrectomy. Transplantation *91*, 457-461.

Oyen 2003

Oyen, O., Andersen, M., Mathisen, L., Kvarstein, G., Edwin, B., Line, P.D., Scholz, T., and Pfeffer, P.F. (2005). Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation *79*, 1236-1240.

Andersen, M.H., Mathisen, L., Oyen, O., Edwin, B., Digernes, R., Kvarstein, G., Tonnessen, T.I., Wahl, A.K., Hanestad, B.R., and Fosse, E. (2006). Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant *6*, 1438-1443.

Simforoosh 2003

Simforoosh, N., Basiri, A., Tabibi, A., Shakhssalim, N., and Hosseini Moghaddam, S.M. (2005). Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int *95*, 851-855.

Wolf 2001

Wolf, J.S., Jr., Merion, R.M., Leichtman, A.B., Campbell, D.A., Jr., Magee, J.C., Punch, J.D., Turcotte, J.G., and Konnak, J.W. (2001). Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation *72*, 284-290.

Fundoplication

Ackroyd 2004

Ackroyd, R., Watson, D.I., Majeed, A.W., Troy, G., Treacy, P.J., and Stoddard, C.J. (2004). Randomized clinical trial of laparoscopic versus open fundoplication for gastro-oesophageal reflux disease. Br J Surg *91*, 975-982.

Chrysos 2002

Chrysos, E., Tsiaoussis, J., Athanasakis, E., Zoras, O., Vassilakis, J.S., and Xynos, E. (2002). Laparoscopic vs open approach for Nissen fundoplication. A comparative study. Surg Endosc *16*, 1679-1684.

Franzen 2005

Franzen, T., Anderberg, B., Wiren, M., and Johansson, K.E. (2005). Long-term outcome is worse after laparoscopic than after conventional Nissen fundoplication. Scand J Gastroenterol *40*, 1261-1268.

Hakanson 2007

Hakanson, B.S., Thor, K.B., Thorell, A., and Ljungqvist, O. (2007). Open vs laparoscopic partial posterior fundoplication. A prospective randomized trial. Surg Endosc *21*, 289-298.

Heikkinen 1999

Heikkinen, T.J., Haukipuro, K., Koivukangas, P., Sorasto, A., Autio, R., Sodervik, H., Makela, H., and Hulkko, A. (1999). Comparison of costs between laparoscopic and open Nissen fundoplication: a prospective randomized study with a 3-month followup. J Am Coll Surg *188*, 368-376.

Heikkinen, T.J., Haukipuro, K., Sorasto, A., Autio, R., Sodervik, H., Makela, H., and Hulkko, A. (2000). Short-term symptomatic outcome and quality of life after laparoscopic versus open Nissen fundoplication: a prospective randomized trial. Int J Surg Investig *2*, 33-39.

Knatten 2012

Knatten, C.K., Fyhn, T.J., Edwin, B., Schistad, O., Emblem, R., and Bjornland, K. (2012). Thirty-day outcome in children randomized to open and laparoscopic Nissen fundoplication. J Pediatr Surg *47*, 1990-1996.

Laine 1997

Laine, S., Rantala, A., Gullichsen, R., and Ovaska, J. (1997). Laparoscopic vs conventional Nissen fundoplication. A prospective randomized study. Surg Endosc *11*, 441-444.

Luostarinen 2001

Luostarinen, M., Virtanen, J., Koskinen, M., Matikainen, M., and Isolauri, J. (2001). Dysphagia and oesophageal clearance after laparoscopic versus open Nissen fundoplication. A randomized, prospective trial. Scand J Gastroenterol *36*, 565-571.

Manchet I

Broeders, J.A., Draaisma, W.A., Rijnhart-de Jong, H.G., Smout, A.J., van Lanschot, J.J., Broeders, I.A., and Gooszen, H.G. (2011). Impact of surgeon experience on 5-year outcome of laparoscopic Nissen fundoplication. Arch Surg *146*, 340-346.

McHoney 2005

McHoney, M., Wade, A.M., Eaton, S., Howard, R.F., Kiely, E.M., Drake, D.P., Curry, J.I., and Pierro, A. (2011). Clinical outcome of a randomized controlled blinded trial of open versus laparoscopic Nissen fundoplication in infants and children. Ann Surg *254*, 209-216.

Nilsson 2000

Nilsson, G., Larsson, S., and Johnsson, F. (2000). Randomized clinical trial of laparoscopic versus open fundoplication: blind evaluation of recovery and discharge period. Br J Surg *87*, 873-878.

Wenner, J., Nilsson, G., Oberg, S., Melin, T., Larsson, S., and Johnsson, F. (2001). Short-term outcome after laparoscopic and open 360 degrees fundoplication. A prospective randomized trial. Surg Endosc *15*, 1124-1128.

Papandria 2015

Papandria, D., Goldstein, S.D., Salazar, J.H., Cox, J.T., McIltrot, K., Stewart, F.D., Arnold, M., Abdullah, F., and Colombani, P. (2015). A randomized trial of laparoscopic versus open Nissen fundoplication in children under two years of age. J Pediatr Surg *50*, 267-271.

Perttila 1999

Perttila, J., Salo, M., Ovaska, J., Gronroos, J., Lavonius, M., Katila, A., Lahteenmaki, M., and Pulkki, K. (1999). Immune response after laparoscopic and conventional Nissen fundoplication. Eur J Surg *165*, 21-28.

Gastric Bypass

Lujan 2004

Lujan, J.A., Frutos, M.D., Hernandez, Q., Liron, R., Cuenca, J.R., Valero, G., and Parrilla, P. (2004). Laparoscopic versus open gastric bypass in the treatment of morbid obesity: a randomized prospective study. Ann Surg *239*, 433-437.

Nguyen 2001

Nguyen, N.T., Goldman, C., Rosenquist, C.J., Arango, A., Cole, C.J., Lee, S.J., and Wolfe, B.M. (2001). Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. Ann Surg *234*, 279-289; discussion 289-291.

Sundbom 2004

Sundbom, M., and Gustavsson, S. (2004). Randomized clinical trial of hand-assisted laparoscopic versus open Roux-en-Y gastric bypass for the treatment of morbid obesity. Br J Surg *91*, 418-423.

Westling 2001

Westling, A., and Gustavsson, S. (2001). Laparoscopic vs open Roux-en-Y gastric bypass: a prospective, randomized trial. Obes Surg *11*, 284-292.

Inguinal Hernia

Abbas 2012

Abbas, A.E., Abd Ellatif, M.E., Noaman, N., Negm, A., El-Morsy, G., Amin, M., and Moatamed, A. (2012). Patient-perspective quality of life after laparoscopic and open hernia repair: a controlled randomized trial. Surg Endosc *26*, 2465-2470.

Aigner 2011

Aigner, F., Augustin, F., Kaufmann, C., Schlager, A., Pratschke, J., and Schmid, T. (2011). Prospective, randomized-controlled trial comparing postoperative pain after open and minimal invasive inguinal hernia repair [abstract]. Eur Surg *43(Suppl 241)*, 39.

Aigner, F., Augustin, F., Kaufmann, C., Schlager, A., Ulmer, H., Pratschke, J., and Schmid, T. (2014). Prospective, randomized-controlled trial comparing postoperative pain after plug and patch open repair with totally extraperitoneal inguinal hernia repair. Hernia *18*, 237-242.

Aitola 1998

Aitola, P., Airo, I., and Matikainen, M. (1998). Laparoscopic versus open preperitoneal inguinal hernia repair: a prospective randomised trial. Ann Chir Gynaecol *87*, 22-25.

Anadol 2004

Anadol, A.Z., Ersoy, E., Taneri, F., and Tekin, E. (2004). Outcome and cost comparison of laparoscopic transabdominal preperitoneal hernia repair versus open Lichtenstein technique. J Laparoendosc Adv Surg Tech A *14*, 159-163.

Andersson 2003

Andersson, B., Hallen, M., Leveau, P., Bergenfelz, A., and Westerdahl, J. (2003). Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: a prospective randomized controlled trial. Surgery *133*, 464-472.

Barkun 1995

Barkun, J.S., Caro, J.J., Barkun, A.N., and Trindade, E. (1995). Cost-effectiveness of laparoscopic and mini-cholecystectomy in a prospective randomized trial (Structured abstract). Surg Endosc *9*, 1221-1224.

Barkun, J.S., Keyser, E.J., Wexler, M.J., Fried, G.M., Hinchey, E.J., Fernandez, M., and Meakins, J.L. (1999). Short-term outcomes in open vs. laparoscopic herniorrhaphy: confounding impact of worker's compensation on convalescence. J Gastrointest Surg *3*, 575-582.

Beets 1999

Beets, G.L., Dirksen, C.D., Go, P.M., Geisler, F.E., Baeten, C.G., and Kootstra, G. (1999). Open or laparoscopic preperitoneal mesh repair for recurrent inguinal hernia? A randomized controlled trial. Surg Endosc *13*, 323-327.

Bektas 2011

Bektas, H., Bilsel, Y., Ersoz, F., Sari, S., Mutlu, T., Arikan, S., and Kaygusuz, A. (2011). Comparison of totally extraperitoneal technique and darn plication of primary inguinal hernia. J Laparoendosc Adv Surg Tech A *21*, 583-588.

Bender 2009

Bender, O., Balci, F.L., Yuney, E., Saglam, F., Ozdenkaya, Y., and Sari, Y.S. (2009). Systemic inflammatory response after Kugel versus laparoscopic groin hernia repair: a prospective randomized trial. Surg Endosc *23*, 2657-2661.

Berndsen 2002

Berndsen, F., Arvidsson, D., Enander, L.K., Leijonmarck, C.E., Wingren, U., Rudberg, C., Smedberg, S., Wickbom, G., and Montgomery, A. (2002). Postoperative convalescence after inguinal hernia surgery: prospective randomized multicenter study of laparoscopic versus shouldice inguinal hernia repair in 1042 patients. Hernia *6*, 56-61.

Bessell 1996

Bessell, J.R., Baxter, P., Riddell, P., Watkin, S., and Maddern, G.J. (1996). A randomized controlled trial of laparoscopic extraperitoneal hernia repair as a day surgical procedure. Surg Endosc *10*, 495-500.

Bharathi 2008

Bharathi, R.S., Arora, M., and Baskaran, V. (2008). Pediatric inguinal hernia: laparoscopic versus open surgery. J Soc Laparoendosc Surg *12*, 277-281.

Bilgin 1997

Bilgin, B., Ozmen, M.M., Zulfikaroglu, B., Cete, M., and Hengirmen, S. (1997). Totally extraperitoneal (TEP) hernia repair versus preperitoneal open repair (PPOR). Surg Endosc *11*, 542.

Bostanci 1998

Bostanci, B.E., Tetik, C., Ozer, S., and Ozden, A. (1998). Posterior approaches in groin hernia repair with prosthesis: open or closed. Acta Chir Belg *98*, 241-244.

Bringman 2003

Bringman, S., Ramel, S., Heikkinen, T.J., Englund, T., Westman, B., and Anderberg, B. (2003). Tension-free inguinal hernia repair: TEP versus mesh-plug versus Lichtenstein: a prospective randomized controlled trial. Ann Surg *237*, 142-147.

Butler 2007

Butler, R.E., Burke, R., Schneider, J.J., Brar, H., and Lucha, P.A., Jr. (2007). The economic impact of laparoscopic inguinal hernia repair: results of a double-blinded, prospective, randomized trial. Surg Endosc *21*, 387-390.

Catani 2003

Catani, M., De Milito, R., Spaziani, E., Chiaretti, M., Manili, G., Capitano, S., Di Filippo, A., and Simi, M. (2003). [Laparoscopic inguinal hernia repair "IPOM" vs "open tension free". Preliminary results of a prospective randomized study]. Minerva Chir *58*, 783-789.

Celebi 2014

Celebi, S., Uysal, A.I., Inal, F.Y., and Yildiz, A. (2014). A single-blinded, randomized comparison of laparoscopic versus open bilateral hernia repair in boys. J Laparoendosc Adv Surg Tech A *24*, 117-121.

Cesana 2011

Cesana, G., Olmi, S., and Croce, E. (2011). Trans-abdominal pre-peritoneal laparoscopic inguinal hernia repair versus classical inguinotomic repair: A randomized study. Surg Endosc *25*, S7.

Champault 1994

Champault, G., Benoit, J., Lauroy, J., Rizk, N., and Boutelier, P. (1994). [Inguinal hernias in adults. Laparoscopic surgery versus the Shouldice method. Controlled randomized study: 181 patients. Preliminary results]. Ann Chir *48*, 1003-1008.

Champault 1997

Champault, G.G., Rizk, N., Catheline, J.M., Turner, R., and Boutelier, P. (1997). Inguinal hernia repair: totally preperitoneal laparoscopic approach versus Stoppa operation: randomized trial of 100 cases. Surg Laparosc Endosc *7*, 445-450.

Chan 2005

Chan, K.L., Hui, W.C., and Tam, P.K. (2005). Prospective randomized single-center, single-blind comparison of laparoscopic vs open repair of pediatric inguinal hernia. Surg Endosc *19*, 927-932.

Chauhan 2014

Chauhan, M., Kumar, A., Munghate, A., and Bawa, A. (2014). Prospective study of open mesh versus laparoscopic mesh repair of inguinal hernia. Surg Endosc *28*, 260.

Colak 2003

Colak, T., Akca, T., Kanik, A., and Aydin, S. (2003). Randomized clinical trial comparing laparoscopic totally extraperitoneal approach with open mesh repair in inguinal hernia. Surg Laparosc Endosc Percutan Tech *13*, 191-195.

Damamme 1998

Damamme, A., Samama, G., D'Alche-Gautier, M.J., Chanavel, N., Brefort, J.L., and Le Roux, Y. (1998). [Medico-economic evaluation of treatment of inguinal hernia: Shouldice vs. laparoscopy]. Ann Chir *52*, 11-16.

Decker 1999

Decker, D., Lindemann, C., Springer, W., Low, A., Hirner, A., and von Ruecker, A. (1999). Endoscopic vs conventional hernia repair from an immunologic point of view. Surg Endosc *13*, 335-339.

Dedemadi 2006

Dedemadi, G., Sgourakis, G., Karaliotas, C., Christofides, T., Kouraklis, G., and Karaliotas, C. (2006). Comparison of laparoscopic and open tension-free repair of recurrent inguinal hernias: a prospective randomized study. Surg Endosc *20*, 1099-1104.

Demetrashvili 2011

Demetrashvili, Z., Qerqadze, V., Kamkamidze, G., Topchishvili, G., Lagvilava, L., Chartholani, T., and Archvadze, V. (2011). Comparison of Lichtenstein and laparoscopic transabdominal preperitoneal repair of recurrent inguinal hernias. Int Surg *96*, 233-238.

Dirksen 1998

Dirksen, C.D., Ament, A.J., Adang, E.M., Beets, G.L., Go, P.M., Baeten, C.G., and Kootstra, G. (1998). Cost-effectiveness of open versus laparoscopic repair for primary inguinal hernia. Int J Technol Assess Health Care *14*, 472-483.

Eklund 2006

Eklund, A., Rudberg, C., Smedberg, S., Enander, L.K., Leijonmarck, C.E., Osterberg, J., and Montgomery, A. (2006). Short-term results of a randomized clinical trial comparing Lichtenstein open repair with totally extraperitoneal laparoscopic inguinal hernia repair. Br J Surg *93*, 1060-1068.

Eklund 2007

Eklund, A., Rudberg, C., Leijonmarck, C.E., Rasmussen, I., Spangen, L., Wickbom, G., Wingren, U., and Montgomery, A. (2007). Recurrent inguinal hernia: randomized multicenter trial comparing laparoscopic and Lichtenstein repair. Surg Endosc *21*, 634-640.

Feliu 2004

Feliu, X., Torres, G., Vinas, X., Martinez-Rodenas, F., Fernandez-Sallent, E., and Pie, J. (2004). Preperitoneal repair for recurrent inguinal hernia: laparoscopic and open approach. Hernia *8*, 113-116.

Filipi 1996

Filipi, C.J., Gaston-Johansson, F., McBride, P.J., Murayama, K., Gerhardt, J., Cornet, D.A., Lund, R.J., Hirai, D., Graham, R., Patil, K., *et al.* (1996). An assessment of pain and return to normal activity. Laparoscopic herniorrhaphy vs open tension-free Lichtenstein repair. Surg Endosc *10*, 983-986.

Fleming 2001

Fleming, W.R., Elliott, T.B., Jones, R.M., and Hardy, K.J. (2001). Randomized clinical trial comparing totally extraperitoneal inguinal hernia repair with the Shouldice technique. Br J Surg *88*, 1183-1188.

Gokalp 2003

Gokalp, A., Inal, M., Maralcan, G., and Baskonus, I. (2003). A prospective randomized study of Lichtenstein open tension-free versus laparoscopic totally extraperitoneal techniques for inguinal hernia repair. Acta Chir Belg *103*, 502-506.

Gong 2011

Gong, K., Zhang, N., Lu, Y., Zhu, B., Zhang, Z., Du, D., Zhao, X., and Jiang, H. (2011). Comparison of the open tension-free mesh-plug, transabdominal preperitoneal (TAPP), and totally extraperitoneal (TEP) laparoscopic techniques for primary unilateral inguinal hernia repair: a prospective randomized controlled trial. Surg Endosc *25*, 234-239.

Gunal 2007

Gunal, O., Ozer, S., Gurleyik, E., and Bahcebasi, T. (2007). Does the approach to the groin make a difference in hernia repair? Hernia *11*, 429-434.

Guner 2009

Guner, A., Guler, K., Bozkurt, S., Kaya, M.A., and Leblebici, I.M. (2009). [Anterior Lichtenstein repair versus posterior preperitoneal repair techniques for recurrent inguinal hernia]. Erciyes Tip Dergisi *31*, 37-43.

Gurbulak 2015

Gurbulak, E.K., Gurbulak, B., Akgun, I.E., Ozel, A., Akan, D., Omerotlu, S., Oz, A., Mihmanli, M., and Bektas, H. (2015). Effects of totally extraperitoneal (TEP) and Lichtenstein hernia repair on testicular blood flow and volume. Surgery *158*, 1297-1303.

Hamza 2010

Hamza, Y., Gabr, E., Hammadi, H., and Khalil, R. (2010). Four-arm randomized trial comparing laparoscopic and open hernia repairs. Int J Surg *8*, 25-28.

Hauters 1996

Hauters, P., Meunier, D., Urgyan, S., Jouret, J.C., Janssen, P., and Nys, J.M. (1996). [Prospective controlled study comparing laparoscopy and the Shouldice technique in the treatment of unilateral inguinal hernia]. Ann Chir *50*, 776-781.

Heikkinen 1997

Heikkinen, T., Haukipuro, K., Leppala, J., and Hulkko, A. (1997). Total costs of laparoscopic and Lichtenstein inguinal hernia repairs: a randomized prospective study. Surg Laparosc Endosc *7*, 1-5.

Heikkinen 1998a

Heikkinen, T.J., Haukipuro, K., and Hulkko, A. (1998). A cost and outcome comparison between laparoscopic and Lichtenstein hernia operations in a day-case unit. A randomized prospective study. Surg Endosc *12*, 1199-1203.

Heikkinen 1998b

Heikkinen, T.J., Haukipuro, K., Koivukangas, P., and Hulkko, A. (1998b). A prospective randomized outcome and cost comparison of totally extraperitoneal endoscopic hernioplasty versus Lichtenstein hernia operation among employed patients. Surg Laparosc Endosc *8*, 338-344.

Inal 2014

Inal, F.Y., Celebi, S., Uysal, A.I., Yilmaz, Y., Toptas, M., and Daskaya, H. (2014). [Comparison of the effects of laparoscopic and open repair techniques on postoperative pain and analgesic consumption in pediatric unilateral inguinal hernia]. Med Bull Haseki *52*, 84-88.

Jess 2000

Jess, P., Schultz, K., Bendtzen, K., and Nielsen, O.H. (2000). Systemic inflammatory responses during laparoscopic and open inguinal hernia repair: a randomised prospective study. Eur J Surg *166*, 540-544.

Juul 1999

Juul, P., and Christensen, K. (1999). Randomized clinical trial of laparoscopic versus open inguinal hernia repair. Br J Surg *86*, 316-319.

Kald 1997

Kald, A., Anderberg, B., Carlsson, P., Park, P.O., and Smedh, K. (1997). Surgical outcome and cost-minimisation-analyses of laparoscopic and open hernia repair: a randomised prospective trial with one year follow up. Eur J Surg *163*, 505-510.

Khan 2013

Khan, N., Babar, T.S., Ahmad, M., Ahmad, Z., and Shah, L.A. (2013). Outcome and cost comparison of laparoscopic transabdominal preperitoneal hernia repair versus open Lichtenstein technique. J Postgrad Med Inst *27*, 310-316.

Khoury 1998

Khoury, N. (1998). A randomized prospective controlled trial of laparoscopic extraperitoneal hernia repair and mesh-plug hernioplasty: a study of 315 cases. J Laparoendosc Adv Surg Tech A *8*, 367-372.

Koivusalo 2009

Koivusalo, A.I., Korpela, R., Wirtavuori, K., Piiparinen, S., Rintala, R.J., and Pakarinen, M.P. (2009). A single-blinded, randomized comparison of laparoscopic versus open hernia repair in children. Pediatrics *123*, 332-337.

Koninger 1998

Koninger, J.S., Oster, M., and Butters, M. (1998). [Management of inguinal hernia--a comparison of current methods]. Chirurg *69*, 1340-1344.

Koninger, J., Redecke, J., and Butters, M. (2004). Chronic pain after hernia repair: a randomized trial comparing Shouldice, Lichtenstein and TAPP. Langenbecks Arch Surg *389*, 361-365.

Kouhia 2009

Kouhia, S.T., Huttunen, R., Silvasti, S.O., Heiskanen, J.T., Ahtola, H., Uotila-Nieminen, M., Kiviniemi, V.V., and Hakala, T. (2009). Lichtenstein hernioplasty versus totally extraperitoneal laparoscopic hernioplasty in treatment of recurrent inguinal hernia - a prospective randomized trial. Ann Surg *249*, 384-387.

Kozol 1997

Kozol, R., Lange, P.M., Kosir, M., Beleski, K., Mason, K., Tennenberg, S., Kubinec, S.M., and Wilson, R.F. (1997). A prospective, randomized study of open vs laparoscopic inguinal hernia repair. An assessment of postoperative pain. Arch Surg *132*, 292-295.

Kunz 1993

Kunz, R., Schwarz, A., and Beger, H.G. (1993). Laparoscopic transperitoneal hernia repair vs shouldice herniorraphy. Preliminary results of a prospective randomized trial. Chir Endosc *Suppl 12*, 12-13.

Lal 2003

Lal, P., Kajla, R.K., Chander, J., Saha, R., and Ramteke, V.K. (2003). Randomized controlled study of laparoscopic total extraperitoneal versus open Lichtenstein inguinal hernia repair. Surg Endosc *17*, 850-856.

Lal 2011

Lal, K., Laghari, Z.H., and Laghari, A. (2011). Laparoscopic total extra peritoneal mesh repair and open Lichtenstein mesh repair for the treatment of inguinal hernia. Quart Med Channel *17*, 13-17.

Langeveld 2010

Langeveld, H.R., Van, T.R.M., Weidema, W.F., Stassen, L.P.S., Steyerberg, E.W., Lange, J., Bonjer, H.J., and Jeekel, J. (2010). Total extraperitoneal inguinal hernia repair compared with Lichtenstein (the level-trial): a randomized controlled trial. Ann Surg *251*, 819-824.

Lau 2006

Lau, H., Patil, N.G., and Yuen, W.K. (2006). Day-case endoscopic totally extraperitoneal inguinal hernioplasty versus open Lichtenstein hernioplasty for unilateral primary inguinal hernia in males: a randomized trial. Surg Endosc *20*, 76-81.

Lawrence 1995

Lawrence, K., McWhinnie, D., Goodwin, A., Doll, H., Gordon, A., Gray, A., Britton, J., and Collin, J. (1995). Randomised controlled trial of laparoscopic versus open repair of inguinal hernia: early results. BMJ *311*, 981-985.

Lawrence, K., McWhinnie, D., Goodwin, A., Gray, A., Gordon, J., Storie, J., Britton, J., and Collin, J. (1996). An economic evaluation of laparoscopic versus open inguinal hernia repair. J Public Health Med *18*, 41-48.

Leibl 1995

Leibl, B., Daubler, P., Schwarz, J., Ulrich, M., and Bittner, R. (1995). [Standardized laparoscopic hernia repair (TAPP) vs. Shouldice repair. Results of a randomized trial]. Chirurg *66*, 895-898.

Leibl, B.J., Daubler, P., Schmedt, C.G., Kraft, K., and Bittner, R. (2000). Long-term results of a randomized clinical trial between laparoscopic hernioplasty and shouldice repair. Br J Surg *87*, 780-783.

Liem 1996

Liem, M.S., van der Graaf, Y., Zwart, R.C., Geurts, I., and van Vroonhoven, T.J. (1997). A randomized comparison of physical performance following laparoscopic and open inguinal hernia repair. Br J Surg *84*, 64-67.

Maddern 1994

Maddern, G.J., Rudkin, G., Bessell, J.R., Devitt, P., and Ponte, L. (1994). A comparison of laparoscopic and open hernia repair as a day surgical procedure. Surg Endosc *8*, 1404-1408.

Mahon 2003

Mahon, D., Decadt, B., and Rhodes, M. (2003). Prospective randomized trial of laparoscopic (transabdominal preperitoneal) vs open (mesh) repair for bilateral and recurrent inguinal hernia. Surg Endosc *17*, 1386-1390.

Bignell, M., Partridge, G., Mahon, D., and Rhodes, M. (2012). Prospective randomized trial of laparoscopic (transabdominal preperitoneal-TAPP) versus open (mesh) repair for bilateral and recurrent inguinal hernia: incidence of chronic groin pain and impact on quality of life: results of 10 year follow-up. Hernia *16*, 635-640.

Merello 1997

Merello, J., Guerra A, G., Madriz, J., and Guerra G, G. (1997). Laparoscopic TEP versus open Lichtenstein hernia repair. Randomized trial. Surg Endosc *11*, 545.

Mesci 2012

Mesci, A., Korkmaz, B., Dinckan, A., Colak, T., Balci, N., and Ogunc, G. (2012). Digital evaluation of the muscle functions of the lower extremities among inguinal hernia patients treated using three different surgical techniques: a prospective randomized study. Surg Today *42*, 157-163.

Moreno-Egea 1999

Moreno-Egea, A., and Aguayo, J.L. (1999). [Totally extraperitoneal laparoscopic surgery versus the Lichtenstein procedure for inguinal hernia repair]. Cir Esp *66*, 53-57.

MRC 1999

MRC (1999). Laparoscopic versus open repair of groin hernia: a randomised comparison. Lancet *354*, 185-190.

Scott, N.W., Grant, A.M., Ross, S.J., Smith, A., Macintyre, I.M.C., and O'Dwyer, P.J. (2000). Patient-assessed outcome up to three months in a randomised controlled trial comparing laparoscopic with open groin hernia repair. Hernia *4*, 73-79.

Naveed 2013

Naveed, M., Zabd-Ur-Rehman, A.R., Javeed, M.U., and Akbar, A. (2013). Comparison of early outcome of laparoscopic with open inguinal mesh hernioplasty. Pak J Med Health Sci *7*, 830-833.

Neumayer 2004

Neumayer, L., Giobbie-Hurder, A., Jonasson, O., Fitzgibbons, R., Jr., Dunlop, D., Gibbs, J., Reda, D., Henderson, W., and Veterans Affairs Cooperative Studies Program, I. (2004). Open mesh versus laparoscopic mesh repair of inguinal hernia. N Engl J Med *350*, 1819-1827.

Ozmen 2004

Ozmen, M.M., Ozalp, N., Zulfikaroglu, B., Soydinc, P., Ziraman, I., and Hengirmen, S. (2004). The evaluation of the peak flow velocity and cross-sectional area of the femoral artery and vein following totally extraperitoneal vs preperitoneal open repair of inguinal hernias. Hernia *8*, 332-335.

Ozmen 2010

Ozmen, M., Zulfikaroglu, B., Ozalp, N., Moran, M., Soydinc, P., and Ziraman, I. (2010). Femoral vessel blood flow dynamics following totally extraperitoneal vs Stoppa procedure in bilateral inguinal hernias. Am J Surg *199*, 741-745.

Paganini 1998

Paganini, A.M., Lezoche, E., Carle, F., Carlei, F., Favretti, F., Feliciotti, F., Gesuita, R., Guerrieri, M., Lomanto, D., Nardovino, M., *et al*. (1998). A randomized, controlled, clinical study of laparoscopic vs open tension-free inguinal hernia repair. Surg Endosc *12*, 979-986.

Payne 1994

Payne, J.H., Jr., Grininger, L.M., Izawa, M.T., Podoll, E.F., Lindahl, P.J., and Balfour, J. (1994). Laparoscopic or open inguinal herniorrhaphy? A randomized prospective trial. Arch Surg *129*, 973-979; discussion 979-981.

Payne 1996

Payne, J., Izawa, M., Glen, P., Grininger, L., Podoll, E., and Balfour, J. (1996). Laparoscopic or tension-free inguinal hernia repair? A cost/benefit analysis of 200 prospectively randomized patients. Surg Endosc *10*, S128.

Picchio 1999

Picchio, M., Lombardi, A., Zolovkins, A., Mihelsons, M., and La Torre, G. (1999). Tension-free laparoscopic and open hernia repair: randomized controlled trial of early results. World J Surg *23*, 1004-1007; discussion 1008-1009.

Pokorny 2008

Pokorny, H., Klingler, A., Schmid, T., Fortelny, R., Hollinsky, C., Kawji, R., Steiner, E., Pernthaler, H., Fugger, R., and Scheyer, M. (2008). Recurrence and complications after laparoscopic versus open inguinal hernia repair: results of a prospective randomized multicenter trial. Hernia *12*, 385-389.

Salma 2015

Salma, U., Ahmed, I., and Ishtiaq, S. (2015). A comparison of post operative pain and hospital stay between Lichtenstein's repair and laparoscopic transabdominal preperitoneal (TAPP) repair of inguinal hernia: a randomized controlled trial. Pak J Med Sci *31*, 1062-1066.

Sarli 1997

Sarli, L., Pietra, N., Choua, O., Costi, R., Thenasseril, B., and Giunta, A. (1997). [Prospective randomized comparative study of laparoscopic hernioplasty and Lichtenstein tension-free hernioplasty]. Acta Biomed Ateneo Parmense *68*, 5-10.

Sarli 2001a

Sarli, L., Villa, F., and Marchesi, F. (2001). Hernioplasty and simultaneous laparoscopic cholecystectomy: a prospective randomized study of open tension-free versus laparoscopic inguinal hernia repair. Surgery *129*, 530-536.

Sarli 2001b

Sarli, L., Iusco, D.R., Sansebastiano, G., and Costi, R. (2001). Simultaneous repair of bilateral inguinal hernias: a prospective, randomized study of open, tension-free versus laparoscopic approach. Surg Laparosc Endosc Percutan Tech *11*, 262-267.

Schrenk 1996

Schrenk, P., Woisetschlager, R., Rieger, R., and Wayand, W. (1996). Prospective randomized trial comparing postoperative pain and return to physical activity after transabdominal preperitoneal, total preperitoneal or Shouldice technique for inguinal hernia repair. Br J Surg *83*, 1563-1566.

Sharma 2013

Dhankhar, D.S., Sharma, N., Mishra, T., Kaur, N., Singh, S., and Gupta, S. (2014). Totally extraperitoneal repair under general anesthesia versus Lichtenstein repair under local anesthesia for unilateral inguinal hernia: a prospective randomized controlled trial. Surg Endosc *28*, 996-1002.

Simmermacher 2000

Simmermacher, R.K.J., Van Duyn, E.B., Clevers, G.J., de Vries, L.S., and van Vroonhoven, T.J.M.V. (2000). Preperitoneal mesh in groin hernia surgery. A randomized clinical trial emphasising the surgical aspects of preperitoneal placement via a laparoscopic (TEP) or grid-iron (Ugahary) approach. Hernia *4*, 296-298.

Singh 2012

Singh, A.N., Bansal, V.K., Misra, M.C., Kumar, S., Rajeshwari, S., Kumar, A., Sagar, R., and Kumar, A. (2012). Testicular functions, chronic groin pain, and quality of life after laparoscopic and open mesh repair of inguinal hernia: a prospective randomized controlled trial. Surg Endosc *26*, 1304-1317.

Sinha 2006

Sinha, R., Sharma, N., Dhobal, D., and Joshi, M. (2006). Laparoscopic total extraperitoneal repair versus anterior preperitoneal repair for inguinal hernia. Hernia *10*, 187-191.

Stoker 1994

Stoker, D.L., Spiegelhalter, D.J., Singh, R., and Wellwood, J.M. (1994). Laparoscopic versus open inguinal hernia repair: randomised prospective trial. Lancet *343*, 1243-1245.

Suter 2002

Suter, M., Martinet, O., and Spertini, F. (2002). Reduced acute phase response after laparoscopic total extraperitoneal bilateral hernia repair compared to open repair with the Stoppa procedure. Surg Endosc *16*, 1214-1219.

Tang 2015

Tang, L.M., Sun, Y.F., Ma, Y.L., Wang, G.H., Huang, H.L., Xu, M.J., and Fei, X.Z. (2015). Comparison of Lichtenstein and laparoscopic transabdominal preperitoneal repair of recurrent inguinal hernias. Eur Surg *47*, S210.

Tanphiphat 1998

Tanphiphat, C., Tanprayoon, T., Sangsubhan, C., and Chatamra, K. (1998). Laparoscopic vs open inguinal hernia repair. A randomized, controlled trial. Surg Endosc *12*, 846-851.

Tomaoglu 2015

Tomaoglu, K., Sari, Y.S., Bektas, H., Koc, O., Gunes, E., Uzum, G., and Kucukyilmaz, M. (2015). Prospective randomized clinical trial of Jean Rives technique versus laparoscopic TEP repair for primary inguinal hernia: 10-year follow-up. Hernia *19*, 383-387.

Tschudi 1996

Tschudi, J., Wagner, M., Klaiber, C., Brugger, J., Frei, E., Krahenbuhl, L., Inderbitzi, R., Husler, J., and Hsu Schmitz, S. (1996). Controlled multicenter trial of laparoscopic transabdominal preperitoneal hernioplasty vs Shouldice herniorrhaphy. Early results. Surg Endosc *10*, 845-847.

Vogt 1995

Vogt, D.M., Curet, M.J., Pitcher, D.E., Martin, D.T., and Zucker, K.A. (1995). Preliminary results of a prospective randomized trial of laparoscopic onlay versus conventional inguinal herniorrhaphy. Am J Surg *169*, 84-89; discussion 89-90.

Wang 2013

Wang, W.J., Chen, J.Z., Fang, Q., Li, J.F., Jin, P.F., and Li, Z.T. (2013). Comparison of the effects of laparoscopic hernia repair and Lichtenstein tension-free hernia repair. J Laparoendosc Adv Surg Tech A *23*, 301-305.

Wellwood 1998

Wellwood, J., Sculpher, M.J., Stoker, D., Nicholls, G.J., Geddes, C., Whitehead, A., Singh, R., and Spiegelhalter, D. (1998). Randomised controlled trial of laparoscopic versus open mesh repair for inguinal hernia: outcome and cost. BMJ *317*, 103-110.

Wennstrom 2004

Wennstrom, I., Berggren, P., Akerud, L., and Jarhult, J. (2004). Equal results with laparoscopic and Shouldice repairs of primary inguinal hernia in men. Report from a prospective randomised study. Scand J Surg *93*, 34-36.

Wright 1996

Wright, D.M., Kennedy, A., Baxter, J.N., Fullarton, G.M., Fife, L.M., Sunderland, G.T., and O'Dwyer, P.J. (1996). Early outcome after open versus extraperitoneal endoscopic tension-free hernioplasty: a randomized clinical trial. Surgery *119*, 552-557.

Yang 2009

Yang, Y.M., and Wang, X.Y. (2009). [Comparison of immune function in children undergoing laparoscopic and conventional inguinal hernia repair]. Chin J Contemp Ped *11*, 490-491.

Zhiping 2007

Zhiping, T., Min, T., and Jin-Cheng, Z. (2007). [Randomized comparative study on totally extraperitoneal prosthetic and tension-free herniorrhaphy]. J Laparosc Surg *12*, 391-393.

Zieren 1998

Zieren, J., Zieren, H.U., Jacobi, C.A., Wenger, F.A., and Muller, J.M. (1998). Prospective randomized study comparing laparoscopic and open tension-free inguinal hernia repair with Shouldice's operation. Am J Surg *175*, 330-333.

Rectal Resection

Araujo 2003

Araujo, S.E., da Silva eSousa, A.H., Jr., de Campos, F.G., Habr-Gama, A., Dumarco, R.B., Caravatto, P.P., Nahas, S.C., da Silva, J., Kiss, D.R., and Gama-Rodrigues, J.J. (2003). Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. Rev Hosp Clin Fac Med Sao Paulo *58*, 133-140.

Arteaga Gonzalez 2006

Arteaga Gonzalez, I., Diaz Luis, H., Martin Malagon, A., Lopez-Tomassetti Fernandez, E.M., Arranz Duran, J., and Carrillo Pallares, A. (2006). A comparative clinical study of short-term results of laparoscopic surgery for rectal cancer during the learning curve. Int J Colorectal Dis *21*, 590-595.

COLOR II

Andersson, J., Angenete, E., Gellerstedt, M., Angeras, U., Jess, P., Rosenberg, J., Furst, A., Bonjer, J., and Haglind, E. (2013). Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial. BJS *100*, 941-949.

van der Pas, M.H., Haglind, E., Cuesta, M.A., Furst, A., Lacy, A.M., Hop, W.C., and Bonjer, H.J. (2013). Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol *14*, 210-218.

COREAN

Kang, S.B., Park, J.W., Jeong, S.Y., Nam, B.H., Choi, H.S., Kim, D.W., Lim, S.B., Lee, T.G., Kim, D.Y., Kim, J.S., *et al.* (2010). Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol *11*, 637-645.

Darai 2010

Darai, E., Dubernard, G., Coutant, C., Frey, C., Rouzier, R., and Ballester, M. (2010). Randomized trial of laparoscopically assisted versus open colorectal resection for endometriosis: morbidity, symptoms, quality of life, and fertility. Ann Surg *251*, 1018-1023.

Fleshman 2015

Fleshman, J., Branda, M., Sargent, D.J., Boller, A.M., George, V., Abbas, M., Peters, W.R., Maun, D., Chang, G., Herline, A., *et al.* (2015). Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes. The ACOSOG Z6051 randomized clinical trial. JAMA *314*, 1346-1355.

Jian 2012

Jian, Z., Chengyu, L., and Xiaoxin, J. (2012). [Laparoscopic vs. open total mesorectal excision for low rectal cancer: randomized controlled trial]. Chin J Min Inv Surg *12*, 27-29.

Leung 2000

Leung, K.L., Kwok, S.P., Lam, S.C., Lee, J.F., Yiu, R.Y., Ng, S.S., Lai, P.B., and Lau, W.Y. (2004). Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet *363*, 1187-1192.

Liang 2011

Liang, X., Hou, S., Liu, H., Li, Y., Jiang, B., Bai, W., Li, G., Wang, W., Feng, Y., and Guo, J. (2011). Effectiveness and safety of laparoscopic resection versus open surgery in patients with rectal cancer: a randomized, controlled trial from China. J Laparoendosc Adv Surg Tech A *21*, 381-385.

Liu 2010

Liu, F.L., Lin, J.J., Ye, F., and Teng, L.S. (2010). Hand-assisted laparoscopic surgery versus the open approach in curative resection of rectal cancer. J Int Med Res *38*, 916-922.

Lujan 2009

Lujan, J., Valero, G., Hernandez, Q., Sanchez, A., Frutos, M.D., and Parrilla, P. (2009). Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. Br J Surg *96*, 982-989.

Maartense 2004

Maartense, S., Dunker, M.S., Slors, J.F., Cuesta, M.A., Gouma, D.J., van Deventer, S.J., van Bodegraven, A.A., and Bemelman, W.A. (2004). Hand-assisted laparoscopic versus open restorative proctocolectomy with ileal pouch anal anastomosis: a randomized trial. Ann Surg *240*, 984-991; discussion 991-982.

Ng 2008

Ng, S.S., Leung, K.L., Lee, J.F., Yiu, R.Y., Li, J.C., Teoh, A.Y., and Leung, W.W. (2008). Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. Ann Surg Oncol *15*, 2418-2425.

Ng 2014

Ng, S.S., Lee, J.F., Yiu, R.Y., Li, J.C., Hon, S.S., Mak, T.W., Ngo, D.K., Leung, W.W., and Leung, K.L. (2014). Laparoscopic-assisted versus open total mesorectal excision with anal sphincter preservation for mid and low rectal cancer: a prospective, randomized trial. Surg Endosc *28*, 297-306.

Pan 2007

Pan, Y.F., Zhang, X.H., Jia, X.J., Qu, J.M., Xiang, Y.Q., Yang, K., Lin, B.R., Zheng, X.F., and Zheng, J. (2007). [Laparoscopic abdominoperineal resection for low rectal cancer]. Zhonghua Wei Chang Wai Ke Za Zhi *10*, 253-256.

Stevenson 2015

Stevenson, A.R., Solomon, M.J., Lumley, J.W., Hewett, P., Clouston, A.D., Gebski, V.J., Davies, L., Wilson, K., Hague, W., Simes, J., *et al.* (2015). Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. JAMA *314*, 1356-1363.

Zhou 2004

Zhou, Z.G., Hu, M., Li, Y., Lei, W.Z., Yu, Y.Y., Cheng, Z., Li, L., Shu, Y., and Wang, T.C. (2004). Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer. Surg Endosc *18*, 1211-1215.

Rectopexy

Boccasanta 1998

Boccasanta, P., Rosati, R., Venturi, M., Montorsi, M., Cioffi, U., De Simone, M., Strinna, M., and Peracchia, A. (1998). Comparison of laparoscopic rectopexy with open technique in the treatment of complete rectal prolapse: clinical and functional results. Surg Laparosc Endosc *8*, 460-465.

Solomon 2002

Solomon, M.J., Young, C.J., Eyers, A.A., and Roberts, R.A. (2002). Randomized clinical trial of laparoscopic versus open abdominal rectopexy for rectal prolapse. Br J Surg *89*, 35-39.