LONG TERM CLINICAL OUTCOMES FOLLOWING LAPAROSCOPIC NISSEN FUNDOPLICATION

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ABSTRACT

The laparoscopic technique of Nissen fundoplication was developed locally and internationally during the early 1990s and remains an established procedure for gastro-oesophageal reflux disease. Reported response rates for the procedure have been consistently higher than for medical treatment with proton pump inhibitors. While a large proportion of patients who have undergone Nissen fundoplication remain symptom-free, a small group of patients experience troublesome symptoms following this procedure such as dysphagia and abdominal bloating. Some authors have suggested that division of the short gastric vessels during this procedure may reduce these symptoms, but progress in the area has been hampered by conflicting data from early and mid-term follow-up intervals. Further, while the current literature suggests the Nissen fundoplication technique has durable efficacy for ten years and beyond, very few studies report data beyond fifteen years follow-up.

The aim of this study was to review the outcome of a large patient cohort who had undergone laparoscopic Nissen fundoplication at up to twenty years of follow-up. Information regarding reflux-related symptoms, medication use, overall satisfaction and quality of life measures was sought to determine the efficacy and tolerability of the procedure at ultra-long term follow-up.

A literature review was completed in March 2016 to locate suitable articles documenting long-term (> ten years) follow-up of patients who had undergone Nissen fundoplication. Various studies of small patient number reported results up to fifteen years of follow-up with one study of fifty-one patients reporting results at twenty years.

The research methodology was approved for use through a local ethics and governance committee. All research was completed within Flinders University's Department of Surgery, located at Flinders Medical Centre. The study involved collation of the twenty-year outcome data from a previous randomised-controlled trial of 102 patients randomised to short gastric division versus non division during laparoscopic Nissen fundoplication. Data was accessed via a surgical unit database containing patient demographic, procedure and outcome information. This database was used to identify suitable individuals who had undergone laparoscopic Nissen fundoplication within the previous twenty-four years. A new assessment tool in the form of a questionnaire containing questions relating to reflux-related symptoms, medications use, overall satisfaction ratings and quality of life measures was sent to patients with a return mail envelope.

From a study population of 252 individuals, clinical outcomes were obtained from 152 respondents with a mean follow-up of 265 months. Study respondents reported a high rate of satisfaction (>85%) with the laparoscopic Nissen fundoplication. Heartburn control remained high with a low incidence of troublesome procedure-related side effects. Outcome data from a subset of the above

patient group showed no advantage from routine division of the short-gastric vessels during fundoplication but was associated with a slightly higher report of abdominal bloat symptoms. A strong correlation was found between typical reflux symptoms with total and symptom-aggregated scores for the disease-specific HRQL survey. In contrast the short-form 36 survey correlated poorly to patient symptom scores.

DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Electronically Signed

Signature

23/07/2019

……...

Date

TERMS AND DEFINITIONS / GLOSSARY

GERD	Gastro-oesophageal reflux disease
GERD-HRQL	GERD health related quality of life questionnaire
GIQLI	Gastrointestinal quality of life index questionnaire
GORD	Gastro-oesophageal reflux disease
GSRS	Gastrointestinal Symptom Rating Scale
HRQoL	Health-related quality of life instrument
H2A	H2-Receptor Antagonist
IQR	Interquartile Range
LOS	Lower Oesophageal Sphincter
LNF	Laparoscopic Nissen Fundoplication
OACIS	Open Architect Clinical Information System
PBS	Pharmaceutical Benefits Scheme
PPI	Proton-Pump Inhibitor
PGWB	Psychological General Wellbeing Scale
PROM	Patient-Reported Outcome Measure
QOL	Quality of Life
RSI	Reflux symptom index
SD	Standard Deviation
SF-36	Short-Form Health Survey/ Rand 36-item Short-Form Survey
SGV	Short Gastric Vessel

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CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

Gastro-oesophageal reflux of acid or bile gastric contents is a physiological process which can be experienced by any individual following a precipitating stimulus. Episodes of reflux may remain asymptomatic or be fleetingly symptomatic with little clinical significance. This process becomes pathological when episodes of acid reflux become frequent or troublesome to the patient. International consensus on the symptomatic definition of GORD remains elusive. Symptoms most commonly attributed to the disease include heartburn (retrosternal pain/burning) or dyspepsia (pain/discomfort in the upper abdomen), acid brash and regurgitation. The Rome criteria was an attempt to refine the definition of functional dyspepsia which could now be categorised as either epigastric pain syndrome or postprandial distress syndrome by Rome III criteria. [1] A multitude of other abdominal symptoms may be attributed reflux disease and include epigastric pain, epigastric bloating or meteorism (gas-bloating) and belching. Some ‘atypical’ symptoms of GORD include voice changes, cough, chest pain, dental caries and recurrent lower respiratory tract infections, and these may show incomplete resolution following antireflux surgery.[2] The somewhat nebulous nature of the disease and its symptomatology contributes to a wide global variation in report of GORD symptoms. A systematic review from 15 studies found the prevalence of at least one symptomatic episode of GORD weekly or more frequently in 10-20% for a Western cohort. [3] In 2005 the overall Australian prevalence of GORD was estimated at 9% based on general practitioner survey data. [4] In comparison, the prevalence in an Asian community was under 5%.[3] Data from a local population sample from South Australia reported approximately half the cohort experiencing some symptom of heartburn with 12% describing frequent symptoms. [5]

A resting pressure gradient of 10 mmHg exists between the stomach and oesophagus. In the absence of key anti-reflux mechanisms, regurgitation of gastric contents into the

oesophagus ensues. The primary mechanical anti-reflux barrier is the lower oesophageal sphincter (LOS). This area of smooth muscle commences in the distal 1-4cm oesophagus and blends with the gastric cardia. It is not a considered a discrete sphincter in most anatomy texts. It is a high pressure zone of the oesophagus that varies depending upon physiological circumstance, being depressed post meal or increased with elevations in intra-abdominal pressure. This is largely via a neuromuscular reflex which is vagally-mediated. It is believed that transient relaxation of the LOS is implicated in most cases of GORD. Other intrinsic anti-reflux mechanisms include the diaphragmatic sphincter, the angle of His (cardio-oesophageal angle) and the phreno-oesophageal ligament. The diaphragmatic sphincter is largely composed of sling-like fibres from the right crus to the diaphragm which provide a 'pinch-cock' mechanism to prevent reflux into the distal oesophagus. Disruption of the phreno-oesophageal ligament promotes a sliding hiatus hernia. The principal effect of the sliding hernia is one of reducing the intra-abdominal component of the oesophagus, limiting any compressive effect from physiological abdominal pressure. The acute angle of His sits below the level of the high pressure zone and provides a minor contribution to the anti-reflux mechanism. In addition, various intrinsic mucosal mechanisms reduce potential damage from refluxed luminal acid. These include mucus-gel, bicarbonate secretion, saliva, peristalsis and multiple intrinsic epithelium mechanisms (buffers, ion channels and electrochemical gradients).

Objective testing is essential during disease workup in GORD, particularly if antireflux surgery is being considered. Conventional endoscopy may show erosive oesophagitis which can support the clinical diagnosis. Nevertheless, endoscopic and other objective testing in patients with symptomatic reflux disease shows considerable variability. [6] At least one-third of symptomatic GORD patients will have normal findings at endoscopy, termed non-erosive GORD. Importantly, a small subgroup of symptomatic GORD patients will have Barrett's metaplasia, a pre-malignant condition which must be confirmed or

excluded during routine workup for reflux symptoms. Twenty-four hour pH monitoring is also a useful baseline study for antireflux surgery workup, particularly when patients remain symptomatic but with normal findings on endoscopy. The detection of abnormal amounts of acid reflux during the monitoring interval supports a diagnosis of GORD. Manometry is another objective test whose primary value is in the diagnosis of oesophageal motility disorders. In a number of treatment centres, the presence of a motility disorder in an individual is a relative contraindication to Nissen fundoplication surgery. However, the utility of the above techniques in patient follow-up following antireflux surgery has been questioned. It has been argued that their invasive nature reduces patient compliance and the results may correlate poorly to patient symptoms. [7]

Pharmacological control remains the most common treatment modality for symptomatic reflux disease. More specifically, the proton-pump inhibitor (PPI) drug class is the most commonly prescribed antireflux medication group in Australia (Pharmaceutical Benefits Scheme data, 2015). Compared to the older H2-receptor antagonist class, PPIs provide superior symptom control and resolution of lower grade oesophagitis on endoscopy. Medication-related side effects are infrequent. Nevertheless, life-long treatment is usually required for continued symptom-relief and their utility in the management of severe oesophagitis grades remains limited. Additionally, a subset of patients fail to achieve adequate control of symptoms (medication-refractory disease). Several randomised trials comparing proton pump inhibitors and Nissen fundoplication have been published. Early studies were limited by initial treatment with H2-receptor antagonists and open Nissen fundoplication surgery. [8] [9] At around six years follow-up, a trial by Spechler et al showed higher reflux control in the surgical treatment arm compared to medication alone. Each treatment arm had similar oesophagitis grades but 62% of surgical patients reported regular antireflux medication use, with the exact indication in most patients uncertain. A recent systematic review comparing laparoscopic Nissen fundoplication and proton-pump

inhibitor therapy collated data from four randomised trials. [10] It found a greater proportion of patients in the surgical treatment groups reported less reflux symptoms in the short and medium term at an expense of higher dysphagia rates. A criticism by the review authors of each contributing trial was a high potential for bias, largely from inadequate blinding and one instance of direct drug-company sponsorship.

Rates of proton-pump inhibitor use following anti-reflux surgery remain significant in the literature, although individual study reporting of their use remains highly variable. In a cohort of 297 objectively-confirmed GORD patients treated with Nissen or Toupet fundoplication with a follow-up of 31 months, 19% of patients were using PPI medication, although only half of this group were using the medication to relieve GORD symptoms.[11] Another study by Madan and Minocha followed 100 patients who had undergone laparoscopic Nissen fundoplication for reflux disease. At the conclusion of the study following three years of clinical follow-up, 53% of patients remained using a PPI. [12] A retrospective review of proton-pump inhibitor use following laparoscopic antireflux surgery across Adelaide hospitals was published by Winjnhoven et al in 2008. In 844 patients with a mean follow-up of 5.9 years, 30% were taking a PPI medication, the majority being prescribed by a general practitioner. [13] In Australia, prescription rates of PPI medications increased by 1318% between 1995 and 2006. [14] Relaxation of Pharmaceutical Benefits Scheme (PBS) restrictions of PPI use in 2001 is a possible reason for this increase. A recent National register-based study of patients who had undergone antireflux surgery in Denmark between 1996 and 2010 was published in 2014. This study showed a marked increase in PPI use in a post-surgical cohort over this time period, with a majority using long-term PPI medication by 10-15 years post-antireflux surgery. [15] Given the above prescription trends in proton-pump inhibitor use, its application as a surrogate measure for surgery outcome remains controversial. The ready availability of the drug class means prescribing by primary care physicians is often for indications other than heartburn

symptoms. A commonly prescribed use is as a gastrointestinal muco-protectant when corticosteroids or non-steroidal anti-inflammatory drugs are administered for a prolonged period. Anecdotal reports from prescribers and patients report use of proton-pump inhibitors for nebulous and widely variable indications such as generalised abdominal pain or to control belching. As such, equating PPI use following Nissen fundoplication to surgical failure is a gross oversimplification.

1.1 The Evolution of Gastro-oesophageal Reflux Surgery

The development of surgery for gastro-oesophageal reflux control began in isolation to that of hiatus hernia repair, whereby a relationship between the two entities was not established until the 1950s. [16] Philip Allison classified hiatus hernia into two types, sliding and para-oesophageal, now referred to as Type I and Type II. Allison's technique of surgical correction involved reduction of the gastric cardia into the abdomen, suturing the phrenoesophageal ligament and peritoneum to the diaphragm and approximation of posterior crural fibres. Short-term results from a cohort of 33 patients showed good efficacy but was offset by high rates of recurrence.[17] Ronald Belsey developed a left posterior transthoracic repair that was initially derived from Allison's technique and designated the Belsey Mark I procedure. This evolved into the Belsey Mark IV incorporating a 240-degree anterior fundoplication. Belsey's central technique involved restoration of the gastric cardia to its normal anatomical location below the diaphragm. A significant paper by Skinner and Belsey was published in 1967 and documented the five-year outcomes of 1030 patients with resolution of reflux symptoms in 85%. However, the method of follow-up employed by Belsey remained vulnerable to bias as clinical outcomes were directly recorded by the treating surgical team. [18] This same year, the eight-year results of another major anti-reflux procedure, the Hill repair (posterior gastropexy), was

published by Lucius Hill. His repair technique involved suturing the phreno-oesophageal membrane to the median arcuate ligament, thereby restoring the angle of His as an anti-reflux barrier. Hill reported symptomatic improvement in 93% of patients, although once again, the nature of clinical follow-up was prone to bias. [19]

1.2 The Nissen Fundoplication Procedure

Rudolph Nissen's technique of fundoplication was first performed in 1955. [20] It employed division of the phreno-oesophageal ligament, mobilisation of the oesophagus without division of the short gastric vessels and a 360-degree fundoplication performed by wrapping the anterior and posterior fundal walls around the distal 5-6 cm segment of oesophagus. To ensure continuity of the gastrointestinal tract, the wrap was performed over an intra-oesophageal bougie. Initial publications reporting outcome data following Nissen fundoplication showed good reflux control. A seminal paper by Demeester and colleagues in 1974 compared the above three techniques in a cohort of medication-refractory GORD patients.[21] Using a prospective study design, forty-five patients were randomised to either Hill, Belsey Mark IV or open Nissen fundoplication. Follow-up was via clinical symptom score and radiographic/pH objective measures. All patients who had undergone Nissen fundoplication had a reduction in their reflux clinical scores compared with 80% for Belsey IV, and 47% Hill repair. The higher clinical response rate in the fundoplication cohort was offset in part by a higher incidence of post-operative dysphagia, although this was similar to the Hill repair cohort. The authors attributed this change to a measured increased oesophageal length which was postulated to limit dilatation of the distal oesophagus in response to a post-swallow food bolus. The subsequent resolution of the dysphagia was deemed to be the body's physiological accommodation to this new oesophageal length. A limitation of this early study was the small study size and wide variation in follow-up (30 -696 days). DeMeester was an early advocate for 24-hour pH

monitoring and manometric techniques as a means of optimising the Nissen fundoplication technique. His study compared these parameters pre- and post-surgery to a control group with no symptoms of reflux. [22] This early research lead to the development of the Demeester and Johnson scoring system to quantify oesophageal acid exposure in symptomatic patients. [23] Using these objective measures, the Nissen procedure was shown to increase LOS pressure and reduce subjective and objective gastro-oesophageal reflux.

Further studies supported the findings of DeMeester and the Nissen fundoplication became the favoured antireflux procedure in most treatment centres. Durable symptomatic control of reflux symptoms in the majority of patients was reported across multiple studies. [22, 24-26]

A multitude of other anti-reflux procedures were developed during this chronological period, many later applied using laparoscopic means. These included the Angelchik prosthesis and ligamentum teres cardiopexy, [27, 28] The Angelchik prosthesis was limited by high rates of prosthesis migration and erosion, troublesome dysphagia and lower rates of reflux control compared to conventional antireflux procedures. [29] A randomised trial comparing teres cardiopexy with open Nissen fundoplication in a medication-refractory GORD cohort showed significantly more recurrent heartburn in the cardiopexy group at one year.[30]

1.3 Laparoscopic Nissen Fundoplication: The technique and uptake in the era of minimal-access surgery

The first laparoscopic Nissen fundoplication was performed by Dallemagne in Belgium in 1991. In a case series of twelve patients with medication-refractory reflux with

oesophagitis and hiatal hernia, nine underwent successful laparoscopic Nissen fundoplication. [31] The procedure employed the placement of five laparoscopic ports to the upper abdomen with initial dissection around the right and left crus to enable reduction of the hiatus hernia with subsequent suture repair. The short-gastric vessels were ligated and the posterior wall of the oesophagus and gastric cardia mobilised fully. The fundal wrap was created over a large-bore nasogastric tube and secured with silk sutures. In three patients conversion to an open procedure was required. Two episodes of conversion to open procedure were attributed to difficulties encountered during dissection of the short gastric vessels. Median length of hospital admission was three days (compared with an accepted six for routine open procedure) and subjectively patients experienced less pain than would be expected for the open procedure. One post-operative pneumonia was recorded and no peri-operative deaths. Two years following his preliminary report, Dallemagne published a case-series of 132 patients who had undergone the laparoscopic Nissen fundoplication procedure. [32] Mean operative times were significantly lower compared to the initial report (117 versus 188 minutes), reflecting a learning curve progression and conversion to open procedure also decreased (3%). Initial post-operative dysphagia was reported in ‘most’ of the treatment cohort. While the authors did not state the exact numbers affected, early dysphagia was said to resolve in all but five percent of patients within one month. A single reoperation was for severe, intractable dysphagia, attributed to a misplaced fundal wrap. Further studies of laparoscopic Nissen fundoplication case-series with short-term follow-up intervals were subsequently published. One four-surgeon case-series by Watson and colleagues used a modification to the original Nissen technique by using a shorter 2cm loose fundal wrap constructed over an oesophageal bougie, while preserving the short-gastric vessels. [33] Their case series of thirty-three patients who had undergone laparoscopic Nissen fundoplication for objectively-confirmed GORD gave similar results to Dallemagne in terms of length of stay

and response rates. Early dysphagia was reported in 10 patients (30%) at one month, with persistent dysphagia at three months in 4 patients (12%). Short-term data from other institutions followed, with multiple small volume case-series showing earlier hospital discharge and comparable or lower complication rates compared with expected norms for the open approach. [34, 35]

The initial findings from pioneering treatment centres undertaking laparoscopic Nissen fundoplication were confirmed by most subsequent randomised trials comparing laparoscopic versus open Nissen fundoplication. These trials showed similar short-term reflux control for both treatment modalities but the laparoscopic treated groups experienced a shorter length of hospital admission and reduced treatment-related side effects such as respiratory and wound complications. These benefits came at a modest cost of increased operating times (typically longer by 30-40 minutes).

The volume of antireflux surgery for GORD increased significantly between 1990 and 1997, with United States data alone showing a near quadrupling of the annual procedure number during this period. [36] This trend was mirrored by national data from other Western countries including Finland over a similar period. [37] United States data from 2005-2010 shows the number of antireflux surgeries to be stable during this interval, albeit at a lower volume from the peak of 16 cases per 100,000 adults in 1999. [38] These studies also indicate a trend towards a higher comorbidity burden in patients undergoing antireflux surgeries. The uptake of proton pump inhibitor medications and more rigorous selection of patients for surgery are two possible explanations for the reduction in antireflux procedures.

1.4 Nissen Fundoplication – Procedure Related Side-Effects

Various procedure-related short and long-term side effects have been attributed to the Nissen fundoplication procedure. These include inability to vomit and belch, flatus, dysphagia, abdominal pain and gas-bloat syndrome, amongst others. Perhaps the most typical 'post-fundoplication' symptoms are those of gas-bloat syndrome and dysphagia. [39] Gas-bloat syndrome is one of the earliest documented side effects following Nissen fundoplication. Somewhat strangely, the term does not yet have a precise definition and is often used interchangeably with the term 'abdominal meteorism'. An over-competent wrap and oesophageal vagal disruption are two potential mechanisms behind its presentation. An early publication of a case-series by Nissen in 1964 estimated the incidence of gas-bloat syndrome post Nissen fundoplication to be 10%.[20] In DeMeester's seminal case series from 1986, the report of gas-bloat was 44% in those patients with normal preoperative distal oesophageal sphincter manometry studies. [22] Gas bloat appears to be less of a feature of studies published since the 1990s, which may reflect adoption of current optimisations to the Nissen fundoplication technique. It is also possible that the term has been somewhat replaced in the surgical lexicon by alternatives in recent studies.

Since the earliest trials comparing clinical outcomes between antireflux procedures, a criticism of the 360-degree fundoplication is that of comparatively high post-operative dysphagia rates. More specifically, both early and late dysphagia has been reported following open or laparoscopic fundoplication, although reported rates vary widely. Similar to gas-bloat syndrome, both a tight fundoplication wrap and denervation of the distal oesophagus have been implicated in its cause. There is also evidence to suggest that dysphagia and gas-bloat, when presenting as new symptoms following fundoplication, impact heavily on patient satisfaction.[40] An early study by Negre reviewed the symptomatic outcome in 226 patients with improvement in reflux symptoms following open

Nissen fundoplication. [41] Following a mean follow-up period of 5.6 years, all patients were found to have experienced some transient postoperative dysphagia with average improvement in the following 3-5 months. At final follow-up, 44% of study participants reported some degree of dysphagia. A review by Lundell reported postoperative early- and late dysphagia rates to be 20% and 5%, respectively. [42] Early dysphagia has been suggested to result from postoperative oedema to the oesophagus, is thought to resolve in a majority of patients and does not predict long-term failure of fundoplication. [43] While the cause of late dysphagia is less distinct, it has been suggested that incomplete lower oesophageal sphincter relaxation may play a role. [44] Late dysphagia is highly variable in that some patients may report mild, occasional or fleeting symptoms with no change in diet. However, a small patient subset (< 5%) may experience daily and/or troublesome dysphagia postoperatively that requires endoscopic or revisional surgery to remedy. [45, 46] It must also be remembered that dysphagia remains a commonly-reported pre-operative symptom in GORD patient cohorts and evaluation of postoperative symptoms need to be placed within this context.

1.5 Modifications to the Nissen fundoplication technique

Nissen fundoplication using either open (conventional) or laparoscopic technique has shown consistent improvement in reflux-related symptom scores in numerous studies. However, a minority of patients experience significant and troublesome side-effects post-procedure. Mechanistically, it is believed that the Nissen fundoplication technique can create an ‘over-competent’ gastro-oesophageal junction, rendering side-effects such as gas-bloat, dysphagia and flatulence post-procedure. Various modifications to Nissen’s technique have been described in the literature as a means of reducing the incidence of these side effects. The Rosetti modification involved the construction of the 360-degree

fundoplication using the anterior wall of the fundus.[47]

1.5.1 Fundoplication technique modifications: The sub-360 degree wrap

Modification to the fundal wrap was first proposed by Toupet in the 1960s and led to the development of the posterior fundoplication with a fundoplication less than 360-degrees. [48] Historically, the Toupet wrap involved a 180-degree arc, but today the most common Toupet repair employs a 270-degree wrap. The major aim behind Toupet's technique was to reduce the incidence of persistent dysphagia following fundoplication which at the time was estimated at 10% following Nissen fundoplication. The basis of his repair was a gastropexy to the hiatal pillars (with no formal closure of any hiatus hernia), posterior mobilisation of the fundus without division of the short-gastric vessels and securing a 180-degree wrap with proximal sutures incorporating diaphragm, stomach and oesophagus. A disadvantage of the Toupet technique is longer procedure time as additional sutures are required to complete the fundoplication. Clinical and objective outcome data at five years follow-up from a prospective randomised trial of Nissen versus Toupet repair showed a significant improvement in heartburn symptoms in both groups with comparable improvements to oesophagitis grading. [49] Dysphagia rates at 5 years were higher in the Nissen cohort, although both groups had a lower post-procedure incidence of dysphagia compared to baseline. Long-term outcomes from a randomised trial at 18 years follow-up comparing Toupet and Nissen-Rosetti techniques did not show any significant difference is heartburn control or side effect profile. [50] The authors suggested that mechanical side effects attributed to the total fundoplication at earlier follow-up may normalise over time.

Multiple partial anterior fundoplication techniques have been described in the literature. The Belsey Mark IV procedure incorporates a 240-degree anterior fundoplication albeit via

a left thoracotomy approach. Alternatives include the Dor procedure, employing an anterior hemi-fundoplication commonly combined with cardiomyotomy for achalasia, and anterior 90-degree and 180-degree fundoplication. Both 90- and 180-degree anterior fundoplications employ hiatal hernia repair and oesophagopexy. The 90-degree partial fundoplication covers the left anterolateral aspect of the oesophagus while the larger 180-degree partial fundoplication is sutured to the oesophagus and right and anterior hiatal rims. Multiple randomised trials have compared both 90-degree anterior partial and to laparoscopic Nissen fundoplication. [51-53] Data from these trials report lower dysphagia rates for the anterior 90-degree fundoplication groups compared to laparoscopic Nissen fundoplication, however this apparent advantage was offset in one trial which reported a higher incidence of heartburn symptoms in the partial fundoplication cohort. Ten-year follow-up data has been reported from a randomised trial comparing anterior 180-degree partial fundoplication to laparoscopic Nissen fundoplication. [54] The authors found no statistically significant differences between either treatment arm in terms of overall satisfaction with surgery, heartburn control, PPI use and side effects such as dysphagia. A trend suggested dysphagia was more likely in the total fundoplication cohort which was offset by a trend toward better heartburn control. Historically a partial fundoplication technique has been preferred for those patients with concurrent GORD and oesophageal motility disorder. However, this has not been fully validated and in limited studies, the Nissen technique has shown some application in patients with poor oesophageal peristalsis. [55, 56]

1.5.2 Fundoplication technique modifications: Division of the short gastric vessels

Donahue and Bombeck described a technique for creation of a ‘floppy’ Nissen

fundoplication by division of the short gastric vessels and full mobilisation of the gastric fundus.[57] The aim of the technique was to prevent reflux of gastric acid contents while allowing for passage of gas and vomitus. From a patient cohort of seventy-seven, follow-up of up to eight years showed increased LOS pressures with subjective resolution of heartburn in 75 patients. One patient remained unable to belch or vomit and another experienced gas-bloat syndrome. [58]

Amongst technique modifications, full mobilisation of the gastric fundus by division of the short-gastric vessels has been an area of controversy in fundoplication surgery for decades. Following the work by Donahue and DeMeester, various authors advocated for the routine division of the short-gastric vessels during fundoplication as a means of reducing postoperative dysphagia. Hunter and colleagues presented a 148 patient case-series of individuals who had undergone laparoscopic Nissen fundoplication, Rosetti-Nissen and Toupet fundoplications with three months of follow-up. The Rosetti-Nissen modification used the anterior fundal wall alone to create the fundoplication. The laparoscopic Nissen fundoplication technique involved ligation of the short-gastric vessels whereas these were preserved in the Rosetti-Nissen fundoplication. Higher rates of persistent moderate to severe dysphagia were reported in the Rosetti-Nissen treated patients compared to the Nissen and Toupet groups (11% vs 2% each).[59] Multiple randomised trials have compared short-gastric vessel division Nissen fundoplication with non-division Nissen fundoplication using the laparoscopic approach. Watson and colleagues published the outcome of a randomised trial comparing short-gastric vessel division laparoscopic Nissen fundoplication versus non-division in a South Australian patient cohort in 1997. [60] No significant differences were found between treatment

groups at six months follow-up. Subsequent follow-up intervals at five- and ten-years have been reported. [61, 62] Outcomes at five-years showed a statistically significant increase in the report of epigastric bloating and inability to belch symptoms in the short-gastric vessel division cohort. Interestingly, this effect seemed to have diminished by ten years of follow-up. There remained no difference in terms of reflux control, overall satisfaction and dysphagia rates between treatment groups. Further randomised trials failed to show any meaningful difference between short-gastric vessel division and non-division cohorts. [63, 64]. The randomised trial by Chysos et al from 2001 showed a similar increase in gas-related bloating symptoms to Watson and colleagues. A subsequent systematic review combining five randomised trials from the area was published in 2011. [65] Pooled meta-analysis did not show any significant difference in terms of reflux control or any treatment-related side effects including gas-related bloat symptoms.

1.5.3 Fundoplication technique modifications: Bougie size and Fundoplication Length

Ongoing research lead to the publication of a significant study by DeMeester et al (1986) where the Nissen technique was modified in a non-randomised fashion in a single-surgeon case-series of 100 patients with objectively-confirmed GORD. Over the course of the study, three modifications to the technique were made with the express intention to reduce post-operative side effects. These were: use of a larger oesophageal bougie, shortening the fundoplication length and full mobilisation of the gastric fundus to construct the fundoplication. These had the effect of reducing transient swallow discomfort, reducing post-operative dysphagia and increasing swallow distal oesophageal relaxation rates, respectively. In particular, a decrease in persistent post-operative dysphagia was marked (21% vs 3%). The construction of a short 2cm fundoplication wrap remains the most widely

accepted modification to the original Nissen technique. DeMeester and colleagues advocated for the use of a 60F bougie to assist in creation of the short fundal wrap. [66] The technique has been associated with durable symptom control and reduced gas-bloat and dysphagia rates.

1.6 Literature Search Process

A literature review was completed in March 2016 to determine literature around the primary clinical question: does laparoscopic Nissen fundoplication have efficacy and favourable side effect profile at twenty years of clinical follow-up? A secondary analysis based on quality of life measures and side effect profile was also posed.

Where possible, the literature review conformed to the principles of a systematic review by PRISMA criteria but exceptions existed. [67] Within the research time and personnel constraints, no registration of the review or duplicate search strategies were made. The literature review was performed by a single investigator under the supervision of multiple experienced research supervisors with regular review via research meetings. Most early research papers in the field were not randomised trials and limiting the search criteria to randomised, blinded trials would have resulted in exclusion of multiple studies with long follow-up. Given the wide range of study designs, quality, study population number and reporting variations, a quantitative assessment using a meta-analysis or similar would be inappropriate. As such, a qualitative analysis was made for each study which was grouped

according to follow-up duration of five to nine years, ten years, fifteen years and twenty years. As a result, this provided a narrative review of the clinical and quality of life outcomes of the Nissen fundoplication procedure for various time points in follow-up.

1.6.1 Key words, terms and databases

A search of the electronic databases ‘MEDLINE’ and ‘PUBMED’ for relevant published articles was undertaken in March 2016. Search terms were limited to those with accepted medical subject headings (MeSH) relevant to the clinical area and included: ‘gastro-oesophageal reflux’, ‘GORD’, ‘GERD’, ‘Nissen fundoplication’. These were combined with relevant subcategory headings and free word combination searches such as ‘outcome’ and ‘long-term’ using keyword search function of each database.

1.6.2 Inclusion and exclusion criteria

Publications consideration for inclusion in review included randomised controlled trials, observational type studies and comparative studies. Articles regarding simple case reports, review articles or those limited to isolated in-vitro research were not included in the review.

Additional Inclusion Criteria:

- Date range between January 1980 and March 2016
- In English language

- Peer reviewed articles

Exclusion Criteria:

- Articles with no English language abstract or main text
- Articles from non-peer reviewed sources
- Articles where surgery performed is not the Nissen type fundoplication
- Articles with results from paediatric cohorts
- Articles with an average patient follow-up (mean or median) less than five years

1.7 Preliminary Search Results - Chronological Progression

The total number of articles retrieved from ‘MEDLINE’ using the subject heading ‘gastro-oesophageal reflux’ with surgery as a subgroup and within the above date constraints numbered 3418. Limiting this search to human, adult subjects reduced this number to 1738 articles. Further limiting the search using the additional subheading ‘outcome’ returned at total of 912. An additional subheading ‘primary’ was included to remove search matches to reoperations, with 139 articles remaining. Given the likelihood of some journal articles matching to ‘fundoplication’ and not ‘gastro-oesophageal reflux’ surgery, an additional search was made using ‘Nissen fundoplication’, returning 1987 results. By limiting this search to the above date range and English literature resulted in 1604 results.

The same search strategy was used for searching the ’Biomed Central’ and ‘PLOS Medicine’ databases. A total of 431 articles mapped to the subject heading ‘gastro-oesophageal reflux surgery’ within Biomed Central. As the search criteria was not able to be limited further, each article and abstract was assessed individually for inclusion in the review. An additional search using the keyword string ‘Nissen fundoplication’ yielded 80 articles which were also considered individually for review inclusion. Using the ‘PLOS Medicine’ database, an initial search using the

keyword string ‘gastro-oesophageal reflux’ returned seven articles. An alternative search using the subject heading ‘Nissen fundoplication outcome’ returned 3255 articles. This search was further refined to include only original articles from peer-reviewed sources and those published within the above date and demographic constraints, yielding 941 results.

Alternative focused search strategies included keyword subject searches using ‘antireflux surgery outcome’ as a grouped keyword string. No relevant articles were retrieved using this search. Further, searches of the above databases using the accepted acronyms ‘GERD’ and ‘GORD’ did not return any additional articles.

In excess of two thousand abstracts were retrieved. Duplicate references and articles not meeting the inclusion criteria were omitted from further analysis. The majority of articles removed from further review were due to short published follow-up intervals, paediatric populations, review articles and where no English abstract or main article text was available.

1.8 Results – Literature Review

A total of fifty-eight articles were included in the review. Searching within ‘MEDLINE’ database retrieved the majority (56 articles) of these references. Two articles from ‘Biomed Central’ matched inclusion criteria and were included in the review. PLOS database searching did not render any further articles.

1.8.1 Literature Review – Five-Nine Year Outcomes

Thirty-four articles detailed clinical follow-up of Nissen fundoplication cohorts between a mean of five and nine years. An additional three articles reported only quality of life outcomes within this follow-up period. Ten articles reported data from randomised trials. The majority of studies (n=24) were case-series studies involving single or multiple surgeons following laparoscopic and/or open

(conventional) Nissen fundoplication. Key elements of data collection were prospective in 11 of these case-series while 13 remained largely retrospective in nature. Table 1.1 summaries the key findings from each study.

1.8.1.1 Randomised trials with Five to Nine Year Outcomes

1.8.1.1.1 Laparoscopic Nissen Fundoplication versus Open Nissen Fundoplication

Two randomised trials investigated laparoscopic Nissen fundoplication versus conventional open Nissen fundoplication for the treatment of GORD. Two reports by Broeders et al provided outcome data between treatment groups at 5 and 9.7 years. [68, 69] The former was borne from a randomised trial from 2000 which was terminated prior to completion owing to concerns the laparoscopic arm of the study had an inappropriately high risk of dysphagia. This led to a cohort study in which surgeon experience for laparoscopic Nissen fundoplication was increased to a minimum of 30 cases, giving a third treatment arm. Dysphagia rates within three months in the second laparoscopic treatment arm were comparable to the conventional Nissen cohort. Draaisma and colleagues' reported the five-year results of this cohort in 2006 [70]. Of the 177 patients randomised in 1997, 148 were available for follow-up at five years which included a structured questionnaire and objective studies (in 97 patients). No differences were found in subjective symptoms, objective rates of acid exposure, reoperation rate or antireflux medication use. Subsequent follow-up of almost ten years for each arm showed comparable improvements in GORD symptoms with similar antireflux medication use. Reintervention rates were significantly higher (35% vs 15%) in the open fundoplication group, largely from incisional herniae.

A similar but smaller randomised trial by Nilsson et al followed sixty patients who were randomised to either laparoscopic Nissen fundoplication or the open technique. [71] Fifty patients were available for follow-up by five years. No difference was found between treatment arms on subjective GORD symptom score or objective testing. One quarter of those in the open treatment arm were dissatisfied with the surgical scar.

1.8.1.1.2 Laparoscopic Anterior Partial Fundoplication versus Laparoscopic Nissen Fundoplication

Two randomised trials investigated laparoscopic anterior (90-degree) fundoplication versus laparoscopic Nissen fundoplication. The local trial by Watson et al randomised 79 patients who were followed with yearly standardised questionnaire. At five years follow-up, outcome data was available for 74 patients. Dysphagia for solids and abdominal bloat symptoms were higher in the Nissen fundoplication group. Antireflux medication use was higher in the anterior fundoplication cohort. Another randomised trial by Nijjar et al was a multi-centre, double-blind design investigating anterior 90-degree partial fundoplication and laparoscopic Nissen fundoplication. From an initial randomisation of 112 patients, 97 were available for follow-up at five years. There was no difference found between treatment groups on overall satisfaction, dysphagia and bloating symptoms but reflux control was superior in the Nissen cohort.

One randomised trial investigated anterior partial (180-degree) versus laparoscopic Nissen fundoplication. [72] This trial by Ludemann et al commenced in 1995 with randomisation of 107 South Australian patients, of which, 101 patients were alive and available for follow-up at 5 years (51 total fundoplication, 50 anterior). The trial found no overall difference in heartburn control and overall satisfaction, although there was a trend toward greater heartburn control at five years with the total fundoplication cohort. This was offset by higher dysphagia score for solids and composite score, as well as abdominal bloat symptoms in total fundoplication.

1.8.1.1.3 Laparoscopic Nissen Fundoplication: Short-Gastric Vessel division versus Non-Division

An early randomised study reporting five-year outcomes in laparoscopic Nissen fundoplication was published by O'Boyle and colleagues in 2002. [61] This study reported outcomes of 102 patients undergoing the procedure with either short-gastric vessel (SGV) division or non-division. During this follow-up period there was no significant difference between the treatment groups in terms of reflux control, overall satisfaction with surgery and dysphagia rates. However, a statistically

significant increase in the report of epigastric bloating and inability to belch symptoms was recorded in the short-gastric vessel division cohort.

1.8.1.1.4 Open Nissen Fundoplication versus Medical Therapy for GORD

The majority of five-year Nissen fundoplication outcome research from the 1990s and early 2000s relates to the open (conventional) technique, reflecting the progressive adoption of the laparoscopic technique early in this period. Two randomised trials by Spechler et al and Lundell et al compared open Nissen fundoplication to continuous medical therapy for the treatment of symptomatic GORD. [9, 73] Both trials showed equivalent quality of life measures at five years, yet the data by Lundell et al demonstrated significantly less treatment failures compared to medical therapy. A similar trial by Spechler and colleagues showed a rate of antireflux medication (62%) and PPI use (32%) following surgery although absolute rates were significantly lower than medically-treated patients and exact frequency of medication use was not stated. Further, the authors did not comment upon the indications behind this medication use in the surgical patient group but it is notable that upon ceasing the medication in the week prior to follow-up endoscopy, any residual GORD symptoms were less severe than the medically-treated patients.

1.8.1.2 Prospective Case Series with Five to Nine Year Outcomes

1.8.1.2.1 Laparoscopic Nissen Fundoplication

Six prospective case-series of laparoscopic Nissen fundoplication were retrieved. Fei et al using a prospective observational type study evaluated the impact of advanced age on outcomes following laparoscopic Nissen fundoplication. A total of 620 (>65yo in 96 participants) patients were enrolled with follow-up beyond 70 months in both groups. Overall clinical follow-up was available in 94%. Although the older cohort experienced more atypical symptoms preoperatively with higher rates of oesophageal motility disorder, similar postoperative outcomes were found in terms of reflux control (>90%) and side effect profile.

Biertho and colleagues prospectively followed 515 patients for five years using a validated questionnaire to investigate the presence of gastrointestinal symptoms following laparoscopic Nissen fundoplication. Unfortunately a large number of patients were not available for follow-up at five years (238 patients, 46%). The procedure was associated with a significant decrease in GORD symptoms but no change in non-specific gastrointestinal symptoms except vomiting.

Anvari et al (2003) and Lafullarde (2001) prospectively followed laparoscopic Nissen fundoplication cohorts in Ontario and South Australia, respectively. [74, 75]The Canadian study followed 332 patients from a single-surgeon series over five years. This study suffered from a high level of incomplete follow-up (181 patients completed follow-up (54%) including objective evaluation). Antireflux medication was prescribed in 12% at five years, although only 5% had abnormal 24-hour pH recordings. Of those who completed follow-up, 86% remained satisfied with the surgical outcome. The local study by Lafullarde and colleagues followed 178 patients who had undergone laparoscopic Nissen fundoplication at a single centre in Adelaide. At a median follow-up of six years, only two patients were lost to follow-up (1%). The vast majority (87%) of patients were reflux-free or reported only occasional mild episodic reflux.

1.8.1.2.2 Mixed Cohort (Laparoscopic Nissen and Partial Fundoplication)

Data published by Engstrom et al in 2012 reported the largest outcome data following antireflux surgery at a mean follow-up of 7.6 years. [76] This prospective case-series had an initial enrolment of 2261 patients, of which 1209 (53%) underwent the Nissen fundoplication procedure. This research from Adelaide utilised local patient outcome data. It should be noted that subsequent chapters of this thesis report longer-term outcomes from patients within this cohort. Engstrom concluded that overall satisfaction scores remained high (>85%) although the authors noted a gradual increase in heartburn visual-analogue scores over the study duration across all surgical treatments. At five-years follow-up, proton-pump inhibitor use by the Nissen fundoplication cohort was reported as 8.8%.

Another large prospective case-series by Brehant and colleagues published in 2006 included 2684

patients who had undergone laparoscopic antireflux surgery (51% Nissen fundoplication) across 31 treatment centres in France. [77] A principal aim of the study was to determine the clinical outcomes following laparoscopic antireflux surgery in elderly patients (>65 years) compared with a younger cohort. Five-year outcome data was available for half of the initial enrolment population, totalling 1363 patients. However, this group represented a mixed surgical group, which included a large proportion who had undergone non-Nissen fundoplications (Partial). No significant difference was demonstrated between the two age groups based on symptoms and functional outcomes.

Three smaller case-series by Granderath et al (2002), Hafez et al (2008) and Simorov (2014) prospectively followed single-centre series of patients who had undergone laparoscopic Nissen fundoplication or Toupet fundoplication for reflux disease. [78-80] In the former study 103 patients were available for follow-up at study completion with reported heartburn resolution in 97%. Reoperation surgery was required in 5% and in half of revision cases dysphagia was considered a major symptom. In the case series by Hafez et al, after a longer median follow-up of 93 months, a higher rate of symptom recurrence (14% vs 9%) was found in the laparoscopic Nissen fundoplication group compared to Toupet fundoplication, without reaching statistical significance. In the study by Simorov et al, data from 297 patients (primarily laparoscopic Nissen fundoplication) was collected prospectively. However, only a small number of patients (40) were available for follow up after 4 years, hence long-term findings are of limited instruction.

A prospective study by Borie et al investigated quality of life measures in GORD patients from a French cohort. [81] All patients underwent laparoscopic Nissen fundoplication for medication-refractory GORD. From an initial accrual of 35 patients, 32 completed six years follow-up which was applied using the Gastrointestinal Quality of Life Index (GIQLI) preoperatively and at set intervals postoperatively. The GIQLI assessment tool is a 36 item measure of quality of life with 50% scoring relating to GORD symptoms. Quality of life estimates were compared to a French population normal value and were significantly lower pre-operatively (98 versus 126 points). The GIQLI scores improved to an average of 108/144 at six years follow-up. Curiously, social dimension score was shown to be lower than at pre-operative over this period of review. GORD Symptoms using the tool was 4% at end of follow-up and 20% patients were using a PPI. The

study by Rebecchi and colleagues also evaluated symptoms and quality of life measures following laparoscopic Nissen fundoplication stratified by gastric emptying rate. [82] Assessments were made using generic Short-Form Health Survey (SF-36), Gastro-oesophageal Health Related Quality of Life (GERD-HRQL) and reflux symptom index (RSI). A total of 172 patients completed follow-up (188 original study number). The study was somewhat unique in demonstrating recurrent weak acid reflux episodes in patients who had undergone fundoplication with preoperative delayed gastric emptying. This finding correlated with poorer symptomatic outcomes but appeared to have minimal effect on quality of life measures.

1.8.1.3 Retrospective Case Series with Five to Nine Year Outcomes

1.8.1.3.1 Laparoscopic Nissen Fundoplication

Six papers reported results from laparoscopic Nissen fundoplication case-series with retrospective study design. Studies by Blazejczyk et al and Kornmo et al suffered from small numbers completing follow-up (29 and 33, respectively), hence results reported were of questionable utility.[83, 84] The analysis by Blazejczyk et al showed a follow-up completion rate of 18% of the institutions case-series compared to 19% (Kornmo et al). Kornmo et al is further hindered by follow-up data which is exclusively from the first 33 patients from the case-series which raises the possibility of a learning-curve bias. Neuvonen et al reported data from a larger cohort of 64 patients which was drawn from a case-series of 107 (follow-up rate 59%) showing heartburn as an infrequent symptom (<10%) at 9.8 years follow-up. This case-series also showed the laparoscopic technique to be associated with a failed fundoplication wrap in 11% at the conclusion of follow-up. The retrospective single-centre case series of Bammer et al (171 patients), Oelschlager et al (288 patients) and Zacharoulis et al (678 patients) were larger studies of individual institutions experience of laparoscopic Nissen fundoplication. [85-87] Average period of follow-up between these studies ranged 60-77 months and all showed high rates of satisfaction and GORD symptoms resolution (>90%). Reports of dysphagia varied considerably, with Zacharoulis et al reporting a troublesome dysphagia rate of 1.8% compared with 27% in Bammer et al analysis. This finding may have been influenced by the manner of recording dysphagia symptoms and incomplete follow-

up (62% at 5 years) in the former study.

1.8.1.3.2 Mixed Cohort (Laparoscopic Nissen and Partial Fundoplication)

Six papers reported five-year outcomes from retrospective case-series reviews of mixed laparoscopic Nissen and partial fundoplication cohorts. Studies by Dassinger et al and Sgromo et al had small volume outcome data (<100 LNF respondents). [88, 89] The largest study from this group was by Pessaux et al with follow-up data from 84% case series (mean 7.1 years) from 1340 patients, 711 of which had undergone laparoscopic total fundoplication.[90] Those undergoing Nissen fundoplication had twice the rates of dysphagia (8%) and gas bloat syndrome (10%) compared to either posterior or anterior partial fundoplication, reaching statistical significance. However, the anterior fundoplication cohort was far smaller than either the Nissen or partial fundoplication groups. Oelschlager et al single-centre case-series also reported a high response rate of 85% in its retrospective analysis. In this series, most patients (>95%) underwent laparoscopic Nissen fundoplication. Durability in reflux control was 77% at 5 years with a minority of patients undergoing 24-hour pH monitoring which confirmed normalisation in 71% tested. Hu et al and Gee et al published smaller case-series from retrospective data reviews of majority laparoscopic Nissen fundoplication cohorts.[91, 92] Unfortunately, follow-up was only complete in 61% and 54%, respectively. Gee et al demonstrated the quality of life GERD-HRQL to approach population norms after five years follow-up post fundoplication. Antireflux medication was recorded at some stage in 43% of respondents. The analysis by Hu et al demonstrated antireflux medication to increase as study follow-up interval increased, although only a minority had objective evidence of recurrent reflux.

1.8.1.3.3 Open Nissen Fundoplication

Luostarienen reported clinical and endoscopic outcomes from his single-centre open Nissen fundoplication case series from Finland in 1993. [26] From a median follow-up of 77 months, 109 patients were available for review (86% of cohort) with most undergoing endoscopic surveillance.

Two thirds were symptom-free. Defective fundoplication on endoscopy correlated with endoscopic findings of esophagitis. Report of dysphagia was high (43%) which may reflect the unmodified Nissen-Rosetti technique used at the time.

Table 1 0-1 Published studies reporting five-year outcomes following Nissen fundoplication. [1] [2]

Author, Date	Patient series (n)	Follow Up, Mean (months)	Selected Findings
Anvari et al 2003 [74]	**181 LNF**	60	Prospective single-surgeon case series. 86% Patient Satisfaction with surgery (5 years). Abdominal bloat 42%. Completed objective investigations – 55%.
Bammer et al [85]	**171 LNF**	77	Retrospective case series, single-centre. Patient Satisfaction 93%, Dysphagia 27%, PPI use 14%.
Biertho et al, 2006 [93]	**515 LNF (277 completed five-year follow-up)**	60	Prospective case series. No significant difference in patients with gastrointestinal symptoms pre- and post-operative. GORD symptoms score significantly lower at 5 years. Vomiting improved.
Blazejczyk et al, 2013 [83]	**29 LNF**	83	Retrospective three-surgeon case series, single-centre. Post-operatively reduced reflux episodes on 24 hr pH monitoring and higher average sphincter pressure. No correlation between DeMeester and GIQLI scores.
Borie et al, 2010 [81]	**32 LNF**	72	Prospective case series. Significantly improved GIQLI score but less than normal population, GORD symptoms reduced 51% to 4%. PPI use 20%.
Brehant et al, 2006 [77]	1363 Mixed LNF and Partial/Anterior Fundoplication	60	Prospective, multi-centre case-series. Comparison 1178 non elderly and 185 elderly patients. No significant difference on dysphagia, recurrence and functional evaluation. Visick 1-2 in 93-94%.
Broeders et al, 2009 [69]	**79 LNF** vs 69 ONF	118	Randomised, multi-centre trial. Relief GORD symptoms 92%. Relief of regurgitation higher in LNF group (99% vs 91%). PPI Rx 27%.
Broeders et al, 2011 [68]	**214 LNF**, 74 ONF, 234 completed follow-up	60	RCT early termination from possible learning curve bias, subsequent prospective cohort study. Outcomes similar between treatments. Visick 1+2 in 90-94% LNF.

[1] Findings expressed in relation to Nissen fundoplication outcomes unless stated. Study number recorded upon follow-up completion, not original enrolment.

[2] *Local trial. Overlap patient group with current study.

Dassinger et al, 2004 [88]	52 patients, majority LNF, minority L Toupet	61	Three surgeon series. Mild or no heartburn in 88%. Moderate-severe dysphagia 16%. Moderate-severe bloating symptoms 39%. QOLRAD mean 5.9 (p 6.0). PPI use 15%.
Draaisma et al, 2006 [70]	**79 LNF** vs 69 ONF	66	Randomised, multi-centre trial. No difference symptom outcome and objective measures. Follow-up manometry and pH monitoring data in 48 LNF + 49 ONF.
Engstrom et al, 2012 [76]	1201 Nissen Fundoplication (majority lap). 1040 Partial F	91	Prospective case series. Would repeat procedure at 5 years in 87%. Mean dysphagia score (solids) = 2 (range 0-10). Significantly higher PPI use with partial fundoplications 23-26% vs Nissen 9%.
Fei et al, 2013 [94]	**589 LNF** (Young <65 and elderly >65 cohorts)	90 (Young) 71 (Elderly)	Prospective observational study. Post-operative manometry showed higher rate impaired oesophageal peristalsis in older cohort. Objective measures within 2 years surgery. Overall outcome scores 89 & 93%.
Gee et al, 2008 [92]	**147 LNF (primary),** 24 Toupet, 18 Redo Surgery	60	Retrospective single surgeon case series. Mean GERD-HRQL score 5.7. Would repeat procedure in 88%. Overall satisfaction 71%
Granderath et al, 2002 [78]	103 Patients (**64 LNF**, 39 Toupet)	60	Prospective case series, single centre. DeMeester score 9.7 at 5 years (68, preop). Objective measures (manometry, pH monitoring) limited to 1 year post surgery.
Hafez et al, 2008 [79]	**89 LNF**, 45 Toupet	60 (min) 93 (median)	Prospective case series, single centre. No significant difference between Nissen and Toupet techniques by symptom control. Recurrence rate for reflux symptoms 14% at 93 months for LNF.
Hu et al, 2013 [91]	187 Nissen (Majority Lap), 8 Partial	76	Retrospective case series, single centre. 45% Reported incomplete heartburn control at follow-up. 82% and 59% Satisfaction at 5 years and 10 years respectively. PPI use 44%.
Kornmo et al, 2008 [84]	**31 LNF** [3]	69 (mid) 117 (long)	Retrospective single surgeon case series. Heartburn symptoms in 16% at long-term follow-up. Bloating symptoms in 52% and 39%; Visick 1-2 93% and 97% at 5 and 10 years, respectively.

Lafullarde et al, 2001 [75]	**166 LNF**	72[4]	Prospective six-surgeon case series, single centre. Heartburn-free 60% at 5 years, Moderate to troublesome heartburn symptoms 13%. Overall satisfaction score 8.2/10. Anti-reflux medication use 11%.
Ludemann et al, 2005 [72]	**51 LNF vs 50 Anterior (180º)**	60	Randomised trial comparing total and 180-degree anterior fundoplication. Nil difference in heartburn control and overall satisfaction. Higher dysphagia (solids) and composite score, bloat in total fundoplication.
Luostarinen et al, 1993 [26]	109 ONF	77	Retrospective case series, single centre study. 67% Heartburn-free at follow-up. Objective investigations showed reflux in 22% patients. 50% patients with reflux symptoms had normal 24 pH recordings. Visick 1-2 in 59%.
Lundell et al, 2001 [73]	122 Open Fundoplication (majority Nissen) vs Medical	60	Randomised, multi-centre study. Lower treatment failure rates with open surgery. QOL measurements equivalent at 5 years.
Neuvonen et al, 2014 [95]	**64 LNF**	118	Retrospective, single centre study. Four surgeon series. Endoscopic follow-up showing 11% defective fundal wrap. Association between defective wrap and heartburn symptoms. Heartburn-free or minimal heartburn in 91%.
Nijjar et al, 2010 [52]	**44 LNF** vs 53 Ant Partial F	60	Prospective randomised study. Symptomatic heartburn in 27% at 5 years. Higher mean heartburn analogue score for anterior fundoplication. Satisfied with outcome in 88%.
Nilsson et al, 2004 [71]	**22 LNF** vs 28 ONF (5 Open Conversion)	60	Prospective randomised study. Symptomatic heartburn 12% at 5 years. No significant differences in subjective or objective outcome measures between groups.
O'Boyle et al, 2002* [61]	**99 LNF**, 50 Non Division vs 49 Short Gastric Division	60	Prospective randomised study. No significant difference in main outcome measures between groups. Heartburn symptoms in 12-18% at 5 years. Visick 1-2 in 70-76%.
Oelschlager et al, 2008 [86]	**288 LNF**	69	Retrospective case series, single-centre study. Symptomatic improvement in heartburn in 90%, complete resolution in 67%. Younger age and male gender predicted symptom resolution.

Oelschlager et al, 2012 [96]	**382 LNF**, 18 Toupet	92	Retrospective case series, single-centre study. GORD symptom control 77% at 5 years. PPI use 37% at study completion.
Pessaux et al, 2005 [90]	**711 LNF**, 559 Toupet, 70 Anterior Partial	85	Retrospective case series multi-centre study. Visick 1-2 93%. Antisecretory medication in 9%.
Rebecchi et al, 2013 [82]	**172 LNF**	60	Prospective case series study. Preoperative mild/moderate delayed gastric emptying associated with recurrent reflux symptoms and return to baseline oesophago-gastric pressures at 5 years.
Simorov et al, 2014 [80]	Primary LNF cohort, 40 with follow-up 6 years+	70	Prospective case series study. Improvement in composite heartburn score 83%.
Sgromo et al, 2007 [89]	**99 LNF** vs 62 Toupet	76	Single centre, two-surgeon series. Reflux symptom-free or significant relief 80%. Equivalent quality of life scores per QOLRAD questionnaire. Anti-reflux medication use 44%.
Spechler et al, 2001 [9]	**38 ONF** vs Medical	109	Randomised trial. No difference between medical therapy and surgery based upon QOL measure, oesophagitis grade and overall satisfaction. Reported regular anti-reflux medication post-surgery 62%.
Watson et al, 2012 [51]	**37 LNF** vs. 37 Anterior (90°) Partial F	60	Randomised trial. Heartburn symptoms in 38% at 5 years. Average visual-analogue heartburn score 2 (range 0-10). Would choose procedure again 76%.
Zacharoulis et al, 2006 [87]	**808 LNF** (130 lost to follow-up, period not stated)	60	Retrospective case series study. Reflux-related symptoms reduced to 5%. Authors reported dysphagia rate diminished by 10 years but follow-up and methods of assessment unclear.

1.8.2 Literature Review – Ten-Fourteen Year Outcomes

A total of seventeen publications reported clinical follow-up at ten to fourteen years following Nissen fundoplication. An additional two articles reported only quality of life outcomes within this follow-up period. Eight studies reported clinical results from randomised clinical trials. The remaining nine articles were case studies, five of which showed part or full prospective data collection. Completeness of follow-up varied considerably between studies, with one study reporting 17% follow-up of objective testing while another reported overall ten-year outcomes from 99% of the original study cohort. In one paper the total number of patients with recorded follow-up could not be ascertained.[97] Table 1.2 summaries the key findings from these studies.

1.8.2.1 Randomised trials with Ten to Fourteen Year Outcomes

1.8.2.1.1 Laparoscopic Nissen Fundoplication versus Open Nissen Fundoplication

The Finnish randomised trial by Salminen et al randomised 110 patients to laparoscopic Nissen fundoplication or open Nissen fundoplication. Eleven year outcomes were published in 2007.[98] A total of eighty-six patients were available for follow-up which consisted of clinical and endoscopic evaluation. Sixteen non-treatment related deaths were recorded. In an attempt to reduce potential for bias, a surgeon independent to the original treating surgical team was involved in follow-up. Objective investigations found more partial or fully disrupted plications in the open cohort compared to laparoscopic arm (40% vs 13%). However, symptom scores remained similar between each group in terms of reflux control and side effect profile. All ten incisional herniae were recorded in the open cohort, although none were requiring surgical fixation at time of review.

1.8.2.1.2 Laparoscopic Anterior Partial Fundoplication versus Laparoscopic Nissen Fundoplication

The randomised trial by Broeders et al was a local study investigating objective outcomes following laparoscopic anterior 180-degree partial fundoplication versus laparoscopic Nissen fundoplication for GORD. [99] Objective follow-up was via oesophageal manometry and 24-hour pH monitoring.

This was a follow-up study to an earlier randomised trial investigating clinical outcomes between fundoplication treatment groups. As per the group's previous follow-up, clinical outcomes were also mapped via a standardised questionnaire. From an initial enrolment of 107 patients, 18 patients were available for objective and clinical follow-up at 14 years (8 anterior, 10 Nissen) while 77 completed clinical assessment. Fourteen non-procedure related deaths were recorded and combined with other exclusion criteria meant 81 patients were eligible for follow-up. Patients from the anterior fundoplication cohort had a higher number of total, weakly acid, mixed and liquid reflux episodes in 24 hours compared to the Nissen cohort, which correlated with a higher rate of symptomatic reflux. Gas-bloat symptoms were similar between groups which was also confirmed in the limited number of patients undergoing objective testing.

Cai and colleagues reported the ten-year clinical outcomes of the above study in 2008. [54] Clinical follow-up was available for 89 patients. No significant differences were found between treatment groups based on reflux control, gas-bloat symptoms, dysphagia or overall satisfaction. However, as noted in other studies, a trend towards better reflux control was found in the Nissen cohort, albeit at the expense of a trend to higher dysphagia rates.

1.8.2.1.3 Laparoscopic Nissen Fundoplication with anterior versus posterior hiatal repair

The local randomised trial by Chew and colleagues published in 2011, investigated the difference in anterior versus posterior hiatal repair in 102 patients undergoing laparoscopic Nissen fundoplication in Adelaide hospitals. [100] Ten-year outcome data was available for 86 patients (43 from each group). Heartburn symptoms remained infrequent (<15%) during the follow-up period, although patients from the anterior hiatal repair group experienced less dysphagia with some foods (lumpy solids 14% versus 39%).

1.8.2.1.4 Laparoscopic Nissen Fundoplication: Short-Gastric Vessel division versus Non-Division

Yang et al published the ten year outcomes from a randomised trial comparing short-gastric vessel division versus non-division during laparoscopic Nissen fundoplication in a South Australian patient

cohort. Earlier outcomes at six months and five years has been reported and at five-years showed a statistically significant increase in the report of epigastric bloating and inability to belch symptoms in the short gastric vessel division cohort. After ten years follow-up, 89 patients provided clinical outcome data with no difference between treatment arms in terms of reflux control, overall satisfaction and dysphagia rates. The earlier association between short-gastric vessel division and gas-bloat symptoms appeared to have diminished. Twenty-year outcome data for this randomised trial is reported in Chapter 6.

A similar Scandinavian study was published in 2009 by Mardani and colleagues. [101] This randomised trial reviewed the clinical outcomes of short-gastric vessel division versus non-division during laparoscopic Nissen fundoplication amongst multiple large treatment centres in Sweden. From an original enrolment of ninety-nine patients, eighty-two patients were available for follow-up using standardised questionnaire. The trial found no statistically significant differences between the two study groups for heartburn control, treatment-related side effects, antireflux medication use or in a health-related quality of life index.

1.8.2.1.5 Open Nissen Fundoplication versus Medical Therapy for GORD

A large multi-centre randomised, controlled trial by Lundell et al investigating clinical outcomes of medical therapy versus antireflux surgery for reflux oesophagitis published results from follow-up at twelve years. [102] Medical therapy utilised omeprazole continuous therapy and surgery was completed by open fundoplication with primarily Nissen technique. Following an original randomisation of 310 patients, 71 medical-treated patients and 53 surgically-treated patients remained for follow-up at twelve years. A greater number of patients in the surgical arm remained in ‘reflux remission’ than in the medical treatment arm. Most treatment failures did not show evidence of oesophagitis on follow-up endoscopy. The study has been criticised by previous authors for its funding which is derived from drug company sponsorship and may represent a conflict of interest. Another potential confounder is the treatment dose of omeprazole, which remained somewhat irregular over the course of the study. The method for ensuring compliance

with PPI therapy involved tablet counting which may be of limited clinical utility.

1.8.2.1.6 Toupet Fundoplication versus Open (Conventional) Nissen Fundoplication

Hagedorn et al reported the results of a randomised trial comparing open Toupet fundoplication with open Nissen fundoplication for the treatment of chronic GORD in 2002. Following an initial enrolment of 137 patients, 110 patients completed follow-up at a median interval of 11.5 years. Eleven patient deaths were recorded which were not attributable to the primary surgery. The trial found no significant difference in terms of reflux control and dysphagia between treatment groups. However, there remained a higher report of postprandial fullness and excess flatus symptoms in the group who underwent Nissen fundoplication. A significantly higher number of patients in the Toupet treatment arm retained the ability to vomit.

1.8.2.2 Prospective Case Series with Ten to Fourteen Year Outcomes

1.8.2.2.1 Laparoscopic Nissen Fundoplication

A single-centre laparoscopic Nissen fundoplication case-series by Cowgill et al reported eleven-year clinical outcomes in 2007. [97] Two perioperative deaths were recorded, both secondary to upper-gastrointestinal perforation. Conversion to open procedure was necessary in 15%. Eighty percent of patients reported resolution or significant improvement in GORD symptoms. The precise number of patients contributing to the study was unclear. The authors identified 29 patients who had died since their procedure from a total of 239 who were selected as the study cohort from a prospective database. The number of patients who were lost to follow-up or had incompletely documented follow-up remain high as the total database number of prospectively followed patients was reported as 829 (incomplete follow-up 72%).

Another case-series by Kelly et al (2007) reported findings of a South Australian cohort who underwent laparoscopic Nissen fundoplication for complicated GORD between 1991 and 1995. Following ten years follow-up, twenty-one patient deaths had been recorded (one procedure-

related) and clinical outcome data was available for 226 patients from an initial 250 identified through a surgical database. Reflux control and overall satisfaction were high, at 84% and 83%, respectively. Reported PPI use was21% and the reoperation rate was 17%. Twenty-year outcomes for a number of patients within this group have been included in this current research and are reported in chapters 3-6.

Morgenthal et al published a case series of laparoscopic Nissen fundoplication reporting the outcomes of 282 patients (312 underwent procedure in the specified follow-up interval). [103] With a mean follow-up of 11 years, 89% of the cohort experienced only mild heartburn or were heartburn-free. Reported daily antisecretory medication use was 30% (including H2 receptor antagonists).

The largest single centre cohort reporting ten-year outcome data was by the Florida research unit of Ross et al. [104] A total of 510 patients with a laparoscopic Nissen fundoplication for GORD were identified as being ten years or longer since primary procedure. Of these 317 patients were available for follow-up at ten years. The durability of the procedure was reflected in positive ten-year results which were comparable to published two-year data. Overall patient satisfaction with the procedure outcome remained high (89%).

1.8.2.2.2 Mixed Cohort (Laparoscopic Nissen and Partial Fundoplication)

The prospective single-surgeon case series by Dallemagne and colleagues (2006) was one of the first articles to report ten-year outcomes from laparoscopic Nissen fundoplication. [105] Data from 68 patients who had undergone the procedure showed 93% to be reflux-symptom free at ten years. The use of proton-pump inhibitor medication was also low (8%).

1.8.2.3 Retrospective Case Series with Ten to Fourteen Year Outcomes

1.8.2.3.1 Mixed Cohort (Laparoscopic Nissen and Partial Fundoplication)

Two retrospective case-series reported clinical outcomes of laparoscopic antireflux surgery at ten

years follow-up. Fein et al reported a single-centre's experience of majority laparoscopic Nissen fundoplication (minority partial and Toupet fundoplication).[106] Objective measures were limited to two years post-procedure. Quality of life assessment was via GIQLI survey. From a total of 134 patients who underwent antireflux procedures, 120 were included in the study. Patients post anterior partial fundoplication showed a higher rate of regurgitation post-procedure. A trend to gas-bloat symptoms was found in the Nissen-treated group, without reaching statistical significance. Antisecretory medication was reported in 28% of the cohort. GIQLI score was significantly higher post-procedure and did not show any significant variation between treatment groups.

Another study by a Spanish single-centre research group (Ruiz-Tovar et al) published the clinical outcome of a retrospective analysis of a laparoscopic Nissen fundoplication and Toupet fundoplication case series. From a total of 116 patients undergoing laparoscopic fundoplication during the time period, 106 patients were included in the study. Reflux control and side effect profile was similar between the Nissen and Toupet fundoplication groups. Overall patient satisfaction for both groups was above 95%. Proton pump inhibitor use was 14%. Clinical follow-up was undertaken by face-to-face interview, although the authors did not state if the clinical staff involved were independent to the original treating surgical team.

1.8.2.3.2 Open Nissen Fundoplication

Two studies reported outcomes at 10 years for open Nissen fundoplication case series using a retrospective study design. The Finnish study by Negre et al reported a single surgeon, single-centre's experience. A total of 94 patients were eligible to participate in the study, of which 60 were included (64%). The authors documented 14 deaths (non-treatment related). Patient follow-up at ten years was conducted by a physician not previously involved in the primary surgery. Abdominal meteroism was reported in 33%, although half of these patients retained the ability to belch. Eighty-one percent of patients remained free of reflux at ten years.

A smaller single-institution open Nissen fundoplication case series was reported by the Italian group of Pidoto et al. From 40 patients who underwent conventional fundoplication for GORD between 1987 and 1994, 25 were included in study follow-up. One death was recorded (non-treatment related). Follow-up was via DeMeester reflux symptom scores, SF-36 and GERD-HRQL quality of life measures. Following 120 month mean follow-up, 68% patients remained asymptomatic and both QOL measures showed average improvement post-procedure. The study reported a high rate of repeat fundoplication (80%) but the authors did not reveal possible reasons behind this result.

Table 1 0-2 Published studies reporting ten-year outcomes following Nissen fundoplication. [1] [2] [3]

Author, Date	Study Number (n)	Follow Up, Mean (months)	Findings
Broeders et al, 2013[99]	**10 LNF** vs 8 Anterior (180°) Partial F	168	Randomised trial. Original trial enrolment 107. Acid reflux in 3/10 LNF cohort. Total number of acid reflux episodes higher in anterior fundoplication group. Mean LOS resting pressure and dysphagia rates were higher in the Nissen group.
Cai et al, 2008[54]	**48 LNF** vs 41 Anterior (180°) Partial F	120	Randomised trial. No significant differences in reflux symptom and side effect profile. Persistent heartburn in 15%. Dysphagia with solids reported in 52%. PPI reported in 19%.
Chew et al, 2011**[100]	**86 LNF** (43 Anterior, 43 Posterior Hiatal Repair)	120	Randomised trial. Heartburn 7-14% at 10 years. Visick 1-2 in 79-86%. Less report dysphagia with solid lumpy foods with Anterior repair (14% vs 39%)
Cowgill et al, 2007[97]	**239 LNF** (12% Redo). Total Database 829.	132	Prospective case series. Frequency and severity of heartburn symptoms significantly reduced. 86% willing to repeat procedure if necessary.
Dallemagne et al, 2006[107]	**68 LNF**, 32 Toupet	123	Prospective single surgeon case-series. 93% reflux symptom free at 10 years. GIQLI scores significantly improved vs medical therapy GORD comparison. Reported PPI use 8%.
Fein et al, 2008[106]	**74 LNF**, 16 Partial, 9 Toupet completed follow-up	120	Retrospective case-series, single-centre. All objective measures within 2 years surgery. High (85%) abdominal bloating symptoms at 10 years. 30% Recurrent heartburn. GIQLI score significantly higher at 10 years than preoperative. 90% Overall Satisfaction.
Hagedorn et al, 2002[108]	54 Nissen-Rosetti (ONF) vs 56 Toupet	138	Randomised trial. Control of heartburn symptoms in 88%. Significantly higher side effects of flatus and postprandial fullness with total fundoplication.

[1] Findings expressed in relation to Nissen fundoplication outcomes unless stated. Study number recorded upon follow-up completion, not original enrolment.
[2] *Local trial. Overlap patient group with current study.
[3] **Local trial. No overlap patient group with current study.

Kelly et al, 2007*[109]	**226 LNF**	120	Prospective, six surgeon case-series. 83% Overall Satisfaction, Visual Analog 7+.(range 0-10). Heartburn-free in 63%. Antireflux medication in 21% at 10 years.
Lundell et al, 2009[102]	53 Open Fundoplication (majority Nissen) vs Medical	144	Randomised, multi-centre clinical trial. Heartburn and regurgitation significantly more common in medical group. Dysphagia more common in surgical cohort. Mean QOL scores similar.
Mardani et al, 2009[101]	**82 LNF** (42 Short gastric vessel division, 40 Non-Division)	120	Randomised clinical trial. Heartburn symptom free in 84%. No clinically significant difference between groups. Antisecretory medication 35%.
Morgenthal et al, 2007[103]	**166 LNF**	132	Prospective case-series, single-centre. Heartburn symptom improved in 90%. Dysphagia defined as 'new' or 'worse' in 20%. Would repeat procedure in 93%. Anti-reflux medication 30% (PPI/H2A)
Negre et al, 1983[25]	60 ONF	120	Retrospective, single-surgeon case-series. Reflux symptom-free 81% at 10 years. Dysphagia 43%.
Pidoto et al, 2006[25, 110]	25 ONF	121	Retrospective case series, single-centre. DeMeester score 1.9 at 10 years (6 preop). Residual heartburn or regurgitation 32%. GERD-HRQL and SF36 improved compared to preop.
Ross et al, 2013[104]	**317 LNF**	120	Prospective case series, single-centre. Frequency and duration of heartburn related symptoms maintained from 2 year data. Cohort satisfied with symptom resolution 89%.
Ruiz-Tovar et al, 2010[111]	56 Nissen F (majority lap.), 50 Toupet	134	Retrospective case series, single-centre. Symptomatic GORD 11%. Dysphagia 20%. Overall satisfaction 96% at 10 years.
Salminen et al, 2007[98]	**49 LNF** vs 37 ONF	137	Randomised clinical trial. Objective measures showed less disrupted plications in LNF (13% vs 40%). Acid-suppressive medication 41%.

Yang et al, 2008*[62]	**88 LNF** (44 Short gastric vessel division, 44 non division)	120	Randomised clinical trial. Reported heartburn symptom 11-18%. Visick 1-2 in 82-88%. Report for most symptoms similar between groups. Patients in non-division group more likely to relieve abdominal bloat by belching.

1.8.3 Literature Review – Fifteen-Nineteen Year Outcomes

Three articles reported long-term follow up between fifteen and nineteen years from two randomised clinical trials and one prospective case series. These are summarised in table 1.3.

1.8.3.1 Randomised trials with Fifteen to Nineteen Year Outcomes

1.8.3.1.1 Toupet Fundoplication versus Open (Conventional) Nissen Fundoplication

The Swedish randomised trial published by Mardani and colleagues in 2011 reported outcomes between posterior partial (Toupet) versus open Nissen fundoplication treatment groups. [50] The operative technique did not necessitate crural repair but short gastric vessels were divided routinely. Initial recruitment was 137 patients with symptomatic GORD, however following a mean follow-up of 18 years, this had reduced to a total of 73 patients (34 Open Nissen and 39 Toupet) available for clinical follow-up. At this late follow-up around 80% of patients remained with heartburn symptom control. No statistically significant difference in side effects was observed, indicating a normalisation with time for any presumed early benefit on side effect profile for the posterior partial fundoplication (if present at all).

1.8.3.1.2 Laparoscopic Nissen Fundoplication versus Open Nissen Fundoplication

Salminen et al published the long-term outcomes from a randomised Finnish trial between laparoscopic Nissen fundoplication versus open Nissen fundoplication. From an original recruitment of 110 patients, 86 completed follow-up at a median of 15.1 years. [112] A significantly higher proportion of patients in the laparoscopic group gave a positive evaluation of surgery compared to the open group (92% versus 76%, p = 0.048). The open fundoplication treated group also experienced a greater number of partial and total disrupted plications (46% vs 11%) and incisional herniae (25% vs 0%). Postoperative proton-pump inhibitor use was 46.5% for the study population, although frequency of administration varied considerably. There was no significant difference in PPI use between the two treatment groups. Amongst patients taking daily proton-pump inhibitor therapy, only half had objective evidence of gastro-oesophageal reflux.

1.8.3.2 Prospective Case Series with Fifteen to Nineteen Year Outcomes

1.8.3.2.1 Laparoscopic Nissen Fundoplication

A single institution's case series reporting the outcomes of the first 100 laparoscopic fundoplication procedures from Florida was published in 2015. [113] Data documenting patient postoperative progress was stored in a surgical database. At a mean follow-up interval of 19 years, 26 patients were confirmed deceased (non-treatment related), while only 27 patients were available for clinical follow-up. Hence, 47 patients were considered lost to follow-up. For these limited patients, overall satisfaction was 95% (sum of subjective rating of 'very satisfied' and 'satisfied'). Given the high number of patients lost to follow-up, the authors reviewed the degree of symptom relief at each patients last documented review which revealed 84% rated symptom relief as 'good' or 'excellent'. However, given the mean length of follow-up for patients lost to follow-up was 62 months, extrapolating these findings to nineteen years seems problematic. Anti-reflux medication use was reported in 55%, with 94% being prescribed by gastroenterologist or primary care doctor without specific indications.

Table 1 0-3 Published studies reporting fifteen-year outcomes following Nissen fundoplication.*

Author, Date	Study Number (n)	Follow Up, Mean (months)	Findings
Mardani et al, 2011[50]	34 ONF, 39 Toupet (Original enrolment 137)	216	Randomised clinical trial. Control of heartburn/regurgitation symptoms 80%. Dysphagia score 4.6, compared with 3.3 for Toupet (non-significant). Able to belch 62%.
Salminen et al, 2012[112]	**48 LNF** vs 38 ONF (110 original enrolment)	181	Randomised clinical trial. Free or mild heartburn/regurgitation symptoms 77%. Dysphagia 31%. Excellent or Good subjective overall surgical result in 80%. Statistical higher positive surgical result LNF > ONF. Total Cohort on daily PPI Rx 10%.
Sandowitz et al, 2015[113]	**27 LNF** (100 original enrolment)	227	Prospective case-series, single-centre. ‘Excellent’ or ‘good’ rating in 84% upon last follow-up. Would repeat procedure in 95%. Anti-reflux medication in 55%.

*Findings expressed in relation to Nissen fundoplication outcomes unless stated. Study number recorded upon follow-up completion, not original enrolment.

1.8.4 Literature Review – Twenty Year Outcomes and Beyond

The review found only two publications reporting outcomes of Nissen fundoplication surgery at 20 years or beyond. Both were case-series studies from relatively small patient cohorts. These are detailed in table 4.

1.8.4.1 Prospective Case Series with Twenty Year Outcomes

1.8.4.1.1 Laparoscopic Nissen Fundoplication

The longest period of follow-up of a laparoscopic Nissen fundoplication cohort was published by Robinson and colleagues in 2014. [114] This data from Portland, Oregan was collected prospectively with subsequent invitation to individuals to complete a survey for 20 year follow-up. From a target cohort of 193 individuals, only 51 completed follow-up, at a median follow-up interval of 19.7 years. Forty patients were recorded as deceased. This represents a response rate of one third when adjusting for patients who were already deceased. Complete control of heartburn symptoms (heartburn and regurgitation) was reported in 74% of respondents. While dysphagia as a daily symptom was recorded in a small proportion (16%), any active symptom of dysphagia was reported in 47%. The vast majority of individuals completing long-term follow-up were satisfied with the fundoplication surgery (90%). Proton pump inhibitors were in current use in 43% although the authors submitted that more than 1 in 5 of this subgroup did not experience heartburn symptoms when off this medication group. Revisional surgery was recorded in 18%. The incomplete follow-up recorded by the majority of the patients in this study remains a weakness and makes interpretation of results problematic.

1.8.4.2 Retrospective Case Series with Twenty Year Outcomes

1.8.4.2.1 Open Nissen Fundoplication

The Finnish research group from the University of Tampere published the twenty-year outcome results from a small cohort of GORD patients who underwent open Nissen fundoplication at a single centre. [115] Study participants underwent surgery during a two-year period in the early 1970s. This retrospective analysis sought follow-up data from 46 patients of which, 25 were available for clinical outcome analysis after a median period of 20 years. Further, most consented to undergo various objective studies including endoscopy, 24-hour oesophageal pH recording/manometry and radio-nucleotide testing. While 92% patients experienced nil or mild heartburn symptoms, overall positive satisfaction in the procedure appeared somewhat disconcordant at 56%. Functional analysis showed a defective fundal wrap in 29% with a trend to reduced lower oesophageal sphincter pressures without reaching statistical significance. Daily or weekly episodes of dysphagia were reported in 16%.

Table 1 0-4 Published studies reporting twenty-year outcomes following Nissen fundoplication.*

Author, Date	Study Number (n)	Follow Up, Mean (months)	Findings
Luostarinen et al, 1993[115]	25 ONF (46 original enrolment)	240	Retrospective case-series, single-centre. Heartburn-free or mild heartburn symptoms in 92%. Satisfaction in 56%; rated procedure 'excellent' or 'good'. Defective fundal wrap in 29% (21 assessed endoscopically). Radio-nucleotide transit test and manometry. Non-significant difference between oesophageal sphincter pressures with intact/defective wrap.
Robinson et al, 2014[114]	**51 LNF** (193 original enrolment)	236	Prospective case-series, single-centre. Complete control of heartburn/regurgitation symptoms in 74%. Overall satisfaction with surgery in 90%. Daily dysphagia in 16%. PPI medication in 43%.

* Findings expressed in relation to Nissen fundoplication outcomes unless stated. Study number recorded upon follow-up completion, not original enrolment.

1.8.5 Literature Review – Quality of Life Long-Term Outcomes

A plethora of quality of life instruments have been utilised in studies of antireflux surgery. These have typically fallen into one of three key categories:

1. Generic quality of life indices
2. Quality of life tools specific to gastrointestinal symptoms
3. Quality of life measures specific to gastro-oesophageal reflux disease.

1.8.5.1 Literature Review – Generic Quality of Life Assessment Tools

A common theme amongst this group of QOL tools is the ability to compare general quality of life data from one cohort to a wider population. A universal generic quality of life instrument is the Medical Outcomes/RAND short-form 36 (SF-36) instrument. In general, responses to the SF-36 questionnaire in GORD patient groups have been shown to correlate poorly to GORD symptoms in a number of studies.

1.8.5.2 Literature Review – Gastrointestinal Symptom-Specific Quality of Life Tools

A number of QOL instruments specific to gastrointestinal symptoms have been developed. For most of these, reflux-related symptoms form a representation within an overall gastrointestinal global measure. Examples include the GIQLI (Gastrointestinal quality of life) and the GSRS (Gastrointestinal Symptom Rating Scale). The GSRS has a longer history of use as a GI symptom-based assessment tool but is not considered by most authors to be a validated QOL instrument. It consists of a 15-item assessment of gastrointestinal symptoms which are each measured on a 7 point scale.

1.8.5.3 Literature Review – Gastro-oesophageal Reflux Disease-Specific Quality of Life Tools

Quality of life measures specific for gastrointestinal reflux disease give the theoretical advantage of linking quality of life measures with disease-specific symptom parameters. Examples include the Gastro-oesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL), QOLRAD (Quality of Life in Reflux Disease and Dyspepsia) and the GERD-TEST (Gastro-oesophageal Reflux and Dyspepsia Therapeutic Efficacy and Satisfaction Test) instruments. Some assessments require a subscription fee for use.

Three articles documented five-year quality of life measures following laparoscopic Nissen fundoplication. All studies involved largely retrospective analysis of outcomes in single-unit case-series populations. A further two studies reported QOL outcomes in largely laparoscopic Nissen fundoplication cohorts at ten years follow-up. All five papers showed high postoperative satisfaction amongst each study group although, somewhat predictably, those with subgroup analysis for ‘dissatisfied’ or ‘treatment failures’ invariably demonstrated lower quality of life scale measures

1.8.5.4 Retrospective Case Series with Five Year Quality of Life Outcomes

1.8.5.4.1 Short-Form (SF-36) & Gastrointestinal Symptom Rating Scale

Studies by Amato et al (2008) and Kellokumpu et al (2013) utilised the SF-36 tool as a quality of life measure. [116, 117] The former combined this with a standardised symptom questionnaire while the latter employed the GSRS (Gastrointestinal Symptom Rating Scale)

tool to provide specific symptom scores. The GSRS has been in use for decades and is composed of five scales of reflux, abdominal pain, diarrhoea, constipation and indigestion. Revicki et al confirmed the validity of the GSRS in the setting of GORD with an American population in the 1990s. [118] However, the GSRS remains a symptom-based assessment tool and has not been validated as a quality of life instrument. [119]The SF-36 was developed by Ware et al in the early 1990s as a generic measure of quality of life. [120] It is now available in over fifty languages and has been applied across a wide range of chronic diseases. The first version is also readily available online without any subscription fee. The SF-36 is divided into eight domains - vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. Scores within each domain are transformed into a 0-100 score and are then standardised against the reference population. A higher score correlates with a greater quality of life. The domains can also be weighted against published transformation coefficients to provide an individual physical component score and mental component score. A study administering the SF-36 in 533 adults with moderate to severe GORD found the disease impacted predominantly on pain, social function and mental health subscales of the SF-36. [121] The analysis by Gee et al linked dysphagia as a side effect post fundoplication to poorer physical scale on the SF-36 tool. [92] However, the three scales of physical, bodily pain and vitality were all improved for the treatment group following laparoscopic Nissen fundoplication. The aforementioned study by Kellokumpu et al showed comparable values for SF-36 domains between the fundoplication cohort and population reference. This variability in findings by various studies using the SF-36 in reflux disease has led to a question of the value of the questionnaire in assessing treatment response. A particular disadvantage of the SF-36 is its lack of specificity, which has been a common criticism in its application to previous trials of reflux disease. Additionally, tabulation of results and transformation of domain data is time-consuming. [122] However, it remains an accessible and widely employed generic QOL instrument, which allows for ready comparison across otherwise disparate populations.

1.8.5.4.2 SF-12 & Quality of Life in Reflux and Dyspepsia (QOLRAD)

A derivation of the short form-36 (SF-36) health survey, the short form-12 (SF-12) was developed as an approximate measure of the SF-36 which could be completed in a shorter time frame. [123] The SF-12 was utilised as a general quality of life survey in the case series by Dassinger et al which also employed the GORD specific quality of life questionnaire (Quality of Life in Reflux and Dyspepsia: QOLRAD). Early development and initial validation of QOLRAD in Europe was completed by Wiklund and colleagues. [124] The QOLRAD questionnaire is a 25-item survey covering the five domains of emotional distress, sleep disturbance, physical and social functioning, eating and drinking, and vitality. The average of each domain is scored with a range of 1-7, the higher value corresponding to better quality of life. [124] [88] The above study by Dassinger and colleagues was a study of seventy-six patients who had undergone laparoscopic Nissen (majority) or partial fundoplication for the treatment of GORD. Following a mean follow-up interval of five years, the patient mean QOLRAD score was similar to the reference population, however, this patient group had a lower mean score for the physical component of the SF-12 compared to the general population

1.8.5.4.3 Gastro-oesophageal Reflux Disease Health-related quality of life (GERD-HRQL) & Derived Health-related quality of life (HRQoL) Scale

Gee and colleagues (2008) applied the GERD-HRQL disease-specific quality of life questionnaire to assess the outcomes of a series of four-hundred and five patients who had undergone primary or revisional laparoscopic fundoplication surgery for GORD. [125] This was developed by Velanovich et al in the mid-1990s as a QOL instrument specific to reflux disease. [126] It is a ten-item assessment with an overall assessment of satisfaction scored

0-45, with zero corresponding to complete satisfaction. Advantages of the GERD-HRQL is its specificity and that it can be completed in a short time-frame.

Neuvonen et al (2014) used an alternative quality of life measure, the HRQoL battery with specific reference to the mean 15D score to assess the ten-year outcomes of a one-hundred and seven patient series who had undergone laparoscopic Nissen fundoplication for reflux in a community hospital. Various earlier studies have employed iterations of the HRQoL battery with probably the earliest application to reflux disease by Mathias et al in 2001. [127] In this early study of medical therapy for non-erosive oesophagitis, the SF-12 instrument was combined with reflux specific questions and generic satisfaction indicators. The above study by Neuvonen et al employed the HRQoL battery and demonstrated a similar result for the mean 15D score of the study population to that of the general population, although data appears to be limited with regard to its overall utility in reflux disease.

1.8.5.4.4 Gastrointestinal quality of life (GIQLI) Scale

The paper by Kamolz et al (2005) of 178 individuals who had undergone laparoscopic Nissen fundoplication with a follow-up of five years, employed the GIQLI (Gastrointestinal quality of life) instrument. [128] This paper reviewed the outcomes of 89 individuals who had undergone laparoscopic Nissen fundoplication without objective oesophagitis to a case-matched group who had undergone surgery with demonstrated oesophagitis. A higher GIQLI score improvement in the non-oesophagitis group was attributed by the authors to a lower preoperative score compared to that of the oesophagitis group. Further, the lower preoperative score in the non-oesophagitis group was postulated by the authors to be due to this group being more sensitive to reflux episodes that the oesophagitis group. The GIQLI instrument was developed by Eypasch et al in the 1990s as a quality of life instrument specific to gastrointestinal diseases. [129] It consists of a 36-item questionnaire with five

response categories including gastrointestinal symptoms, physical symptoms, psychological and social items. A limitation of the GIQLI instrument is that is not specific to reflux disease but merely gastro-intestinal disease in general. It is available online and can be accessed via subscription payment.

The ideal instrument for measuring quality of life would shows high validity, reliability and responsiveness. Chassany et al define validity, specifically construct validity as ‘the extent to which an instrument measures what it is intended to measure’, reliability as ‘the degree to which an instrument gives similar scores on repeated administrations’ and responsiveness as an innate ability to ‘detect changes over time’. [119] Confirmation of the validity of a given GORD QOL instrument remains problematic as no clear reference standard exists for comparison. Most of the above instruments were originally validated using reference indicators such as the SF-36 and other non-specific QOL surveys. Accessibility could also be added as a measure of effectiveness of a QOL instrument. Any significant cost burden in utilising any QOL survey for research purposes is likely to provide a significant barrier to uptake. It is within this context that a quality of life instrument is selected for follow-up of patients with GORD.

Table 1 0-5 Published studies reporting quality of life measures five to ten-year outcomes following Nissen fundoplication.

Author, Date	Study Number (n)	Follow Up, Mean (months)	QOL Instrument	Findings
Amato et al, 2008[116]	**102 LNF** Target n=144	60.1	SF-36	SF-36 and Standardised symptom questionnaire. Significant reduction in sym compared to preoperative. Bodily pain remained below control. 6% severe dy
Gee et al, 2008[92]	**173 LNF** (primary) Target n=405	60	GERD-HRQL	Retrospective case-series analysis. GERD-HRQL 5.71 (mean). Satisfied in 7
Kamolz et al, 2005[128]	**178 LNF**	60	GIQLI	Oesophagitis negative and positive case matched analysis. Higher GIQLI outc 95%.
Kellokumpu et al, 2013[117]	139 (Majority Lap. Nissen) Study n=249, Target n=180	120	SF-36	SF-36 similar to age-matched general population except for treatment failures
Neuvonen et al, 2014[130]	**64 LNF** Target n=107	120	HRQoL	HRQoL. Mean 15D score for patient group similar to population. 36% PPI me

1.9 Literature Review - Key Findings

- Open Nissen Fundoplication has durable efficacy in controlling symptoms of reflux (>80%), with high patient satisfaction at up to twenty years follow-up.
- Laparoscopic Nissen Fundoplication has durable efficacy in controlling symptoms of reflux (> 80%) at up to ten years follow-up and possibly beyond. A minority of patients experience troublesome dysphagia at ultra-long term follow-up.
- Laparoscopic posterior partial fundoplication (incl. Toupet) does not confer any consistent advantage in side effect profile at long term follow-up (5-10 years) compared with laparoscopic Nissen fundoplication
- Laparoscopic anterior partial fundoplication does not confer any consistent advantage in side effect profile at long term follow-up (5-10 years) compared with laparoscopic Nissen fundoplication
- Quality of life data following laparoscopic Nissen fundoplication is limited to ten years follow-up and correlation with clinical symptoms is variable. There is no local data in this treatment setting.
- The SF-36 appears to be the most widely employed QOL instrument in GORD follow-up
- Routine division of the short gastric vessels (SGV) during laparoscopic Nissen fundoplication does not appear to confer any advantage to ten years follow-up.
- The association between division of short gastric vessels (SGV) during laparoscopic Nissen fundoplication and abdominal bloat type symptoms has conflicting evidence
- Reporting of proton pump inhibitor prescription following laparoscopic Nissen fundoplication is highly variable, appears to be increasing, but data following ten years follow-up, particular at a local level is lacking.

1.5 Gaps in the Literature

- Laparoscopic Nissen Fundoplication symptom control at 20 years follow-up (subjectively termed ‘ultra-long’ term). Local data in this treatment setting. Proton pump inhibitor use at ultra-long term follow-up remains unknown.
- Quality of life data following laparoscopic Nissen fundoplication beyond 10 years follow-up. Local data in this treatment setting is lacking, as is any correlation between general and disease-specific QOL tools with clinical symptom scoring.

- Data for short-gastric vessel division during laparoscopic Nissen fundoplication at 20 years follow-up and comparison with non-division.

1.6 Summary

This literature review of Nissen fundoplication long-term clinical and quality of life outcomes has revealed the evolution of the technique as it moved from the open or conventional technique to the now-accepted laparoscopic procedure. A plethora of short and medium-term clinical follow-up has been published on the laparoscopic technique since its adoption in the early 1990s. The durability of the technique in terms of heartburn symptom control appears to be similar for both short and long-term follow-up. However, variations in reported incidence of treatment-related side effects such as dysphagia and abdominal bloating symptoms, combined with a well-documented increase in prescription of proton-pump inhibitor medications with longer follow-up intervals casts doubt upon the procedure as a long-term ‘cure’ for gastro-oesophageal reflux disease. Further, a distinct lack of published quality of life outcomes at extended follow-up intervals up to twenty years post-surgery limits assessment of the technique in a broader context. New research reporting twenty-year clinical and quality of life outcomes in a large cohort of patients following laparoscopic Nissen fundoplication would be a positive contribution to this area of research and would aim to address some of the shortfalls in research around the technique. The forthcoming chapter describes the methodology used to develop a novel study in this area, which aims to address some of these key research deficiencies.

CHAPTER 2 METHODOLOGY AND METHODS

The long-term outcome following laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease (GORD) is of material interest to both patients and clinicians. A better understanding of the late-term outcomes of the procedure also has implications on health-care planning and resource allocation. Within this context, determining the optimal place of surgery for reflux disease is crucial, yet the data reporting clinical outcomes beyond ten years follow-up is sparse. The research collaboration between the Upper Gastrointestinal units of the major teaching hospitals in metropolitan Adelaide, namely Flinders Medical Centre, The Royal Adelaide Hospital and The Queen Elizabeth Hospital, as well as various private hospitals has contributed to a common surgical audit database. This has been prospectively maintained by a small core group of surgeons who were local pioneers of the laparoscopic Nissen fundoplication technique since 1991. The identification of patients from this audit who have undergone surgery at twenty years or longer prior to the study commencement underpins this research. By identifying suitable patients in this audit database, clinical follow-up data on GORD symptoms, surgical satisfaction ratings and other information could be collected via study questionnaire. In this manner a descriptive study was completed to determine the long-term clinical outcomes of laparoscopic Nissen fundoplication.

Potential alternative research methodology includes robust study designs such as randomised controlled trials and prospective cohort studies. While these established study designs have scope for high quality research, both are limited by long periods required for patient accrual. This becomes further problematic when one considers the largest volume of laparoscopic Nissen fundoplication procedures were completed during the mid-1990s to early 2000s, both internationally and locally, making this large patient group ineligible for inclusion in such prospective studies. A descriptive study design was selected as this was most suitable to address the above research needs. In particular, it would permit the inclusion of this large patient cohort and could be applied within the timeframe necessary for a research higher degree project.

Assessment of outcomes following anti-reflux surgery has been traditionally approached using objective, symptom-related or quality of life assessments. Objective testing can involve invasive procedures such as gastroscopy, oesophageal manometry and 24-hour pH studies. These investigations seek to assess for improvement in aspects such as oesophagitis grade, frequency of acid-reflux episodes or normalisation of physiological endo-luminal upper gastrointestinal pressures. For a significant number of patients objective procedures are poorly tolerated, particularly pH monitoring. The uptake of these investigations is further limited in symptom-free patients, as performing such procedures is of limited tangible benefit from an individual patient perspective. Symptom-related assessments may be recorded by patients or clinicians following anti-reflux surgery. As clinician-reported symptom outcomes (particularly those from the primary surgeon) are fraught with potential bias, these are rarely reported. Patient-Reported Outcome Measures (PROMS) are completed by the patient and often utilise validated symptom-based scores and overall treatment measures. Global scoring for each symptom and outcome parameter is often assessed using visual-analogue scoring systems. These may be further combined with quality of life questionnaires, of which many different assessment tools have been utilised in GORD patient groups.

The use of a study instrument in the form of a validated questionnaire documenting patient reflux symptoms, surgical side effects, global surgical outcome ratings and medication use, amongst others, has been used previously by the local research group with good patient acceptance. Further, the quality of life outcomes have been measured using established generic and specific instruments in the form of the short-form 36 (SF-36) and Gastro-oesophageal Reflux Health-Related Quality of Life (GERD-HRQL) questionnaires.

The completion of this descriptive study from patients recruited using the local, prospectively-maintained surgical audit database is believed to provide the largest clinical follow-up data at twenty-years following laparoscopic Nissen fundoplication.

2.1 Research Aims

2.1.1 Primary Aim

To determine the long-term efficacy of laparoscopic Nissen fundoplication for the control of symptoms of gastro-oesophageal reflux disease (GORD).

2.1.2 Secondary Aims

To determine the quality of life at late follow-up following laparoscopic Nissen fundoplication.

To determine the efficacy and tolerability of routine division of the short gastric vessels during laparoscopic Nissen fundoplication.

To determine the use of anti-reflux medication at late follow-up following fundoplication.

2.1.3 Hypotheses

1. Laparoscopic Nissen fundoplication provides sustained control of reflux symptoms at late (10-20+ years) follow-up.

2. Laparoscopic Nissen fundoplication reduces the need for long-term anti-reflux medication.

3. Laparoscopic Nissen fundoplication does not have a deleterious effect upon the quality of life at late term (10-20+ years) follow-up.

4. The routine division of the short-gastric vessels during laparoscopic Nissen fundoplication has no effect on procedure-related symptoms.

2.2 Methods

2.2.1 Study Questionnaires

Patient reported outcome measures (PROMS) were assessed using a structured questionnaire adapted from a patient outcome assessment tool in use within the Flinders Department of Surgery.

2.2.1.1 Study Questionnaires - Clinical Outcome Questionnaire

The survey evaluated post-operative symptoms in each key symptom areas of heartburn, regurgitation and dysphagia. Numerical visual-analogue scoring was used for quantification of symptom severity in preference to Likert scales. The reason for this was previous experience from the Department of Surgery in applying visual-analogue scales in similar questionnaires and a concern than Likert scales may not reflect the same linearity.[131]

Heartburn: Assessed by visual-analogue score (range 0-10) 10= severe heartburn, 0 = no heartburn. Frequency assessed via radio button selection for: 'Never', 'Occasionally', 'Monthly', 'Weekly', 'Daily' or 'Each Meal'.

Heartburn *severity* **AFTER** surgery (**NOW)**

0----1----2----3----4----5----6----7----8----9----10

(0=no heartburn) (10=severe heartburn)

Heartburn *frequency* **AFTER** surgery (**NOW)**

☐Never ☐Occasionally ☐ Monthly ☐Weekly ☐Daily ☐Each Meal

Regurgitation: Assessed by visual-analogue score (range 0-10) 10= severe regurgitation, 0 = no regurgitation. Frequency assessed via radio button selection for: 'Never', 'Occasionally', 'Monthly', 'Weekly', 'Daily' or 'Each Meal'.

Regurgitation *severity* **AFTER** surgery (**NOW)**

0----1----2----3----4----5----6----7----8----9----10

(0=no regurgitation) (10=severe regurgitation)

Regurgitation *frequency* **AFTER** surgery (**NOW)**

☐Never ☐Occasionally ☐ Monthly ☐Weekly ☐Daily ☐Each Meal

Dysphagia: Assessed via YES/NO question to 'Do you have difficulty swallowing or does food or liquids stick in your food pipe/gullet?'

Frequency of dysphagia assessed using radio button selection: 'Never', 'Occasionally', 'Monthly', 'Weekly', 'Daily' or 'Each Meal'.

Severity of dysphagia assessed using visual-analogue (range 0-10) 10= severe difficulty, 0 = no difficulty. Assessed individually for both liquids and solids.

Difficulty swallowing *frequency* **AFTER** surgery (**NOW)**

☐Never ☐Occasionally ☐ Monthly ☐Weekly ☐Daily ☐Each Meal

Difficulty in swallowing **LIQUIDS**

severity **AFTER** surgery (**NOW)**

0---1----2----3----4----5----6----7----8----9----10

(0=no difficulty) (10=severe difficulty)

Difficulty in swallowing **SOLIDS**

severity **AFTER** surgery (**NOW)**

0---1----2----3----4----5----6----7----8----9----10

'Other' Symptoms

The breadth of possible symptoms experienced following antireflux surgery was addressed by check box selection of any or all symptoms which were currently experienced post procedure.

Please tick the boxes below ☑ to indicate any *other* symptoms you have **now**:

AFTER surgery **(NOW)**	Symptoms
☐	Pain around top of stomach region
☐	Pain on swallowing
☐	Fullness in the stomach after eating or early fullness with eating
☐	Unable to belch or burp
☐	Bloating of the stomach
☐	Inability to relieve bloating *(If you suffer from bloating)*
☐	Nausea *(feeling sick)*
☐	Vomiting
☐	Coughing at night
☐	Wheezing at night
☐	Choking attacks at night
☐	Increased passage of wind from the bowel
☐	Diarrhoea *(loose bowel motions)*
☐	Chest pain
☐	Shortness of breath
☐	I don't have any of these symptoms

Most Significant Symptom: Assessed via a free-text response to the following question:

Which **ONE** of these symptoms troubles you ***most CURRENTLY*** (including heartburn, difficulty in swallowing and regurgitation)? _____

Antireflux Medication Use: Assessed via YES/NO question. ‘Are you taking any medications for heartburn?’

Followed by checkbox selection for commonly used antireflux medication including primary proprietary name and free-text for any medications not listed.

☐Esomprazole (Nexium®)	☐Cimetidine (Magicul®)	☐AluTab®
☐Lansoprazole (Zoton®)	☐Famotidine (Pepzan®)	☐Gaviscon®
☐Omeprazole (Losec®)	☐Nizatidine (Tazac®)	☐Mylanta®
☐Pantoprazole (Somac®)	☐Ranitidine (Zantac®)	☐Tums®/Rennie®/Salvital®
☐Rabeprazole (Pariet®)		☐Other Antacid
		☐Sucralfate (Ulcyte®)

If you are taking any other medication for heartburn which is not listed, please tell us what it is;
……

……

Satisfaction with Surgery: Four parameters addressed global satisfaction with surgery. These were:

An overall assessment of surgical outcome rated as ‘Poor’, ‘Fair’, ‘Good’ or ‘Excellent’.

A modified-Visick score (range 1-5).

Visick 1 = No symptoms

Visick 2 = Mild symptoms easily controlled by simple care

Visick 3 = Moderate symptoms not controlled by simple care but not interfering with social life or work

Visick 4 = Moderate symptoms interfering with social life or work

Visick 5 = Symptoms as bad or worse than prior to surgery.

A visual-analogue score (range 0-10), completely satisfied = 10, completely dissatisfied = 0

A question regarding decision for surgery: Having gone through this operation and knowing now what is involved, would you have made the same decision to have the same operation for the same problem (In other words, do you think you made the correct decision when you agreed to have the operation)?

2.2.1.2 Study Questionnaires – Quality of Life Outcomes

The RAND/MOS Short-Form 36 (SF-36) version 1 was used as a generic quality of life assessment tool.

The GERD-HRQL disease-specific assessment was used for a reflux-specific QOL measure.

The above questionnaires were selected for use in the study as they were deemed to give the best balance of the ideal study questionnaire parameters in terms of high validity, reliability and responsiveness, yet are able to be used free of any subscription fees. The SF-36 is a widely employed instrument which allows for comparison across studies using generic quality of life data. Local population normal values also permit comparison in the absence of baseline QOL values. The GERD-HRQL disease-specific questionnaire has an established history of use in similar studies of reflux disease and has been shown to closely reflect the typical symptoms of GORD.[132]

2.2.2 Participation criteria

In order to collect clinical outcome data for twenty-years follow-up post laparoscopic Nissen fundoplication, all participants were required to have undergone the procedure prior to 1997. This included the full cohort from the aforementioned short gastric division versus non-division in laparoscopic Nissen fundoplication trial. Further, as the technique was adopted locally by Adelaide treatment centres in 1991, the study population was derived from those patients who had

undergone the procedure between 1991 and 1996 (inclusive).

2.2.3 Participant Recruitment

Baseline demographic and treatment details for the majority of patients who had undergone anti-reflux surgery in Adelaide metropolitan hospitals had been previously recorded within a surgical audit database maintained through the Flinders Medical Centre and Royal Adelaide Hospitals. The surgical unit database uses Filemaker Pro (Apple Inc.) software and stores demographic, preoperative, comorbidity, operative, and outcome data. It is maintained by a dedicated research associate within the research division of surgery of Flinders University. Using this database, the research team were able to identify potential study participants who had undergone a primary laparoscopic Nissen fundoplication procedure between 1991 and 1996 (inclusive). This patient group was invited to participate in the study by mail.

2.2.4 Participant Population

The patient cohort consisted of individuals who had undergone a laparoscopic Nissen fundoplication operation at Flinders Medical Centre, the Royal Adelaide Hospital, and private hospitals treating patients managed by the same FMC and RAH surgeons across the above time period.

2.2.5 Inclusion criteria

- Underwent a laparoscopic Nissen fundoplication procedure at least twenty years ago.

2.2.6 Exclusion criteria

- Unable to speak English.
- Unable to complete the questionnaire because of known intellectual or cognitive impairment.
- Deceased.

- Where basic demographic or operative data was lacking and/or such information could not be readily verified by other means.
- Where patient has previously refused further new study participation.

Exclusion criteria was checked using information contained in OACIS (the South Australian hospital patient information system) and the surgical audit database. Additional information obtained through some patients contributing to previous randomised trials was also cross-referenced against exclusion criteria.

2.2.7 Study Design

Descriptive Study of twenty-year clinical outcomes following laparoscopic Nissen fundoplication

Study Process

1. Identification of Suitable Study Participants
    - Review of surgical audit database to determine patients who have had laparoscopic Nissen fundoplication surgery and at least twenty years follow-up.
    - Review database, and OACIS to check inclusion and exclusion criteria

2. Mail information sheet and questionnaire to Participants

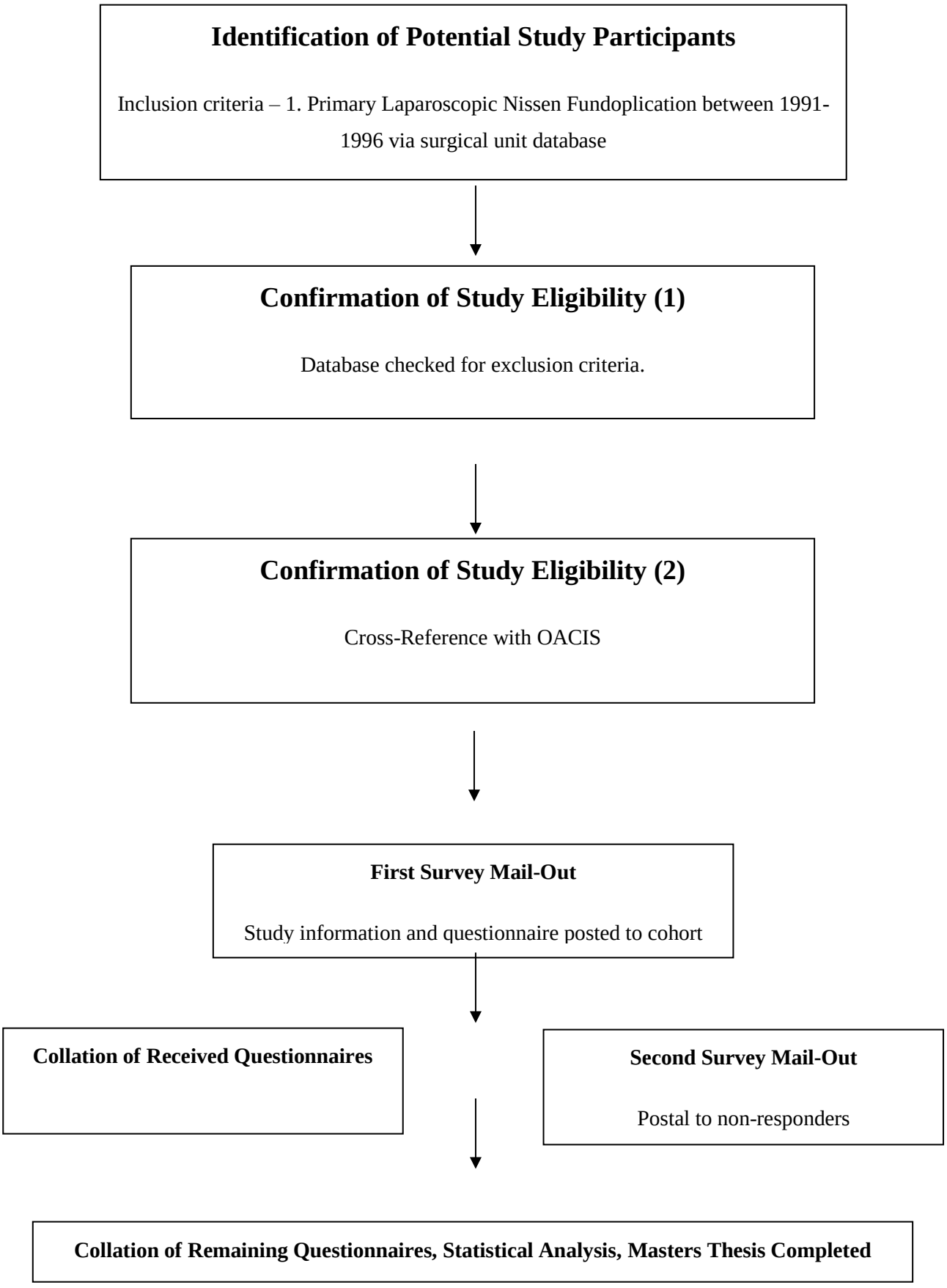
3. Receipt of completed questionnaires

4. Second mail-out one month later to individuals who have not returned the questionnaire. Telephone contact where possible if no response after 2 mail-outs

5. Collation of participant responses and analysis of data

6. Write up and submit papers to journals, and research thesis (MS for Dr Kinsey-Trotman)

2-1 Study Design



2.2.8 Ethical Considerations

All research was conducted in accordance with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research guidelines (update May 2015).

The study protocol and accompanying material was approved for use by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) who deemed it met the requirements of the National Statement on Ethical Conduct in Human Research, application number 110.16, dated April 27, 2016.

Study participants reserved the right to withdraw their participation from the study at any point until research submission.

2.2.9 Data Analysis

All patient information data was stored in a secured computer database (FileMaker Pro version 13; FileMaker Inc) within the department of surgery at Flinders Medical Centre which was co-located with Flinders University. Data was stored in patient re-identifiable form using a unique identifier.

All statistical analysis was undertaken using SPSS version 23 and 25 (International Business Machines, IBM 2016). Mann-Whitney U-test (two-tailed) used to assess for differences between non-parametric data. Fisher's exact test used to compare nominal values via contingency table analysis. Tests of correlation used Spearman rank testing. Basic data handling and calculations was completed using Excel 2013 (Microsoft corporation).

2.3 Summary

This study sought to address the deficit in clinical data following laparoscopic Nissen fundoplication

outcomes at long-term follow-up beyond ten years. The study population was drawn from the large patient base who underwent the procedure locally during the 1990s. By using existing prospective surgical database information, the study was able to readily identify suitable patients to form the study cohort. The use of a questionnaire to map clinical outcome data was combined with quality of life instruments in the short-form 36 (SF-36) version 1 and disease-specific GERD-HRQL. This enabled ready comparison with baseline clinical information of symptom scores and gave an indication as to the overall durability of the procedure at long-term follow-up. The quality of life data was able to be compared to published local population data and provide an alternative assessment as to the overall surgical outcome.

CHAPTER 3 STUDY PARTICIPANT OUTCOMES VERSUS NON-PARTICIPANTS. INTERNAL VALIDITY

3.1 Demographic Information

A fundamental question regarding a research cohort is how representative are those individuals to that of the entire intervention population from which they are derived? In order to address this question a sub-study was created comparing the population chosen for inclusion in the study to those individuals who were excluded. To this end the surgical unit database was searched for the most recent clinical outcome data for each patient who was not included in the current study. A comparison was then made between demographic, operative and outcome data between the two patient groups.

A total of 252 individuals were included in the initial study mail-out. This represented 62.8% of the total database population (401) who had undergone laparoscopic Nissen fundoplication with minimum demographic and operative data recorded between 1991-1996. A total of 149 patients (37.1%) were not included in the study. Amongst this patient group, fifty-four patients were recorded as deceased. A further ninety-two had previously refused or been lost to follow-up. The remaining three patients were unsuitable for study involvement owing to acquired physical or mental incapacity.

The patient group excluded from the current study showed a significantly higher proportion of females compared to the study population (49% versus 34%, P = 0.002). This patient group were of similar age (mean 67.6 versus 67.0 years, P = 0.291) and of higher baseline body-mass index (28.5 versus 27.1 kg/m2. P = 0.033) than the study population. Demographic data is summarised in table 3-1.

Table 3-1 Demographic Data by Study and Non-Study Population

PARAMETER	MAILED	NOT MAILED	P
NUMBER	252	149	
DEMOGRAPHIC INFORMATION			
MALE	168 (66%)	76 (51%)	**0.002**

FEMALE	84 (33%)	73 (49%)	
AGE (MEAN) CURRENT-ALIVE, years	67 (SD 12.0)	67.6 (14.8)	0.291
AGE (MEDIAN) CURRENT – ALIVE, years	67 (IQR 17.2)	67 (24)	
AGE (MEAN) OP, years	45 (SD 12.0)	51.1 (16.0)	**0.001**
AGE (MEDIAN) OP, years	46 (IQR 16.5)	53 (26.5)	
BASELINE BMI, MEAN (kg/m2)	27.1 (SD 4.9)	28.5 (4.9)	**0.033**
BASELINE BMI MEDIAN (kg/m2)	26.9 (IQR 5.7)	28.5 (6.8)	

3.2 Procedural Information

The mean procedure time was similar for both patient groups (95.7; SD 40.2 versus 91.6 mins; SD 39.1, P = 0.108), excluded and included patients, respectively. The presence of a hiatal hernia was documented in a higher proportion of patients from the excluded cohort (57% versus 45%, P = 0.017). The operative technique was modified around 1994 for routine hiatal hernia repair during the period relevant to the database population. This involved routine posterior hiatal hernia suture repair for all laparoscopic Nissen fundoplication procedures. As such a greater number of patients underwent formal hiatal hernia repair (74% versus 67%, P = 0.216). Both excluded and included patient populations were exposed to this change in practice.

A significantly higher proportion of non-study patients underwent division of the short gastric vessels during fundoplication compared to the study population (25% versus 15%, P = 0.012). This

was also reflected in a trend towards longer operative times (4.1 mins) in the non-study cohort, without reaching statistical significance. The rate of conversion to open procedure was twice the rate compared to the survey population (12% versus 6%, P = 0.062). Procedural information for study and non-study cohorts is summarised in table 3-2.

Table 3-2 Procedural Variables by Study and Non-Study Population

PARAMETER	STUDY COHORT	EXCLUDED	P
NUMBER	252	149	
PROCEDURE VARIABLES			
HIATAL HERNIA	114 (45%)	85 (57%)	**0.017**
HERNIA REPAIR CONFIRMED	170 (67%)	110 (74%)	0.216
NON-DIVISION SHORT GASTRICS	215 (85%)	111 (75%)	**0.012**
SHORT GASTRIC VESSEL DIVISION	37 (15%)	37 (25%)	
OPEN CONVERSION	16 (6%)	18 (12%)	0.062
PROCEDURE TIME (MINS)	91.6 (SD 45.9)	95.7 (40.2)	0.108
PROCEDURE TIME (MEDIAN)	80 (IQR 45)	85 (55)	

3.3 Surgical Complications and Revisional Surgery

Overall surgical complications were reported in 31 patients (21%) from the excluded cohort compared to 37 (15%) in the study population (P = 0.130). Owing to the shorter follow-up interval of the excluded patients, the analysis of complication and revisional surgery was limited to ten years follow-up.

Stratification based on intraoperative, early post-operative (within 30 days) and late (31 days to 10 years) complications did not reveal any significant difference between the two groups.

Revisional surgery was required in 29 patients (20%) from the excluded cohort and 33 patients (13%) from the study cohort within the above follow-up constraints. No statistically significant difference was found between groups based on absolute revisional surgery number or following stratification by time.

Table 3-3 Complication and Revisional Surgery Data by Study and Non-Study Population

PARAMETER	STUDY COHORT	EXCLUDED	P
NUMBER	**252**	**149**	
	COMPLICATION DATA		
TOTAL COMPLICATIONS BY INDIVIDUAL PATIENT	37 (15%)	31 (21%`)	0.130
COMPLICATION INTRAOPERATIVE	10 (4%)	4 (3%)	0.584
COMPLICATION <31 DAYS	21 (8%)	9 (6%)	0.439

COMPLICATION LATE (31 DAYS TO 10 YEARS)	22 (9%)	18 (12%)	0.303
	REVISIONAL SURGERY		
EARLY REVISION <31 DAYS	8 (3%)	10 (7%)	0.133
LATE REVISION 31 DAYS TO 10 YEARS	25 (10%)	19 (13%)	0.410

3.4 Admission Data

Mean and median length of stay was similar between both cohorts. The non-study group had a mean length of stay of 4.2 days (SD 2.6) compared to study participants of 3.8 days (1.9). Median length of stay was 3 days for both groups; 3 days (IQR 2) vs 3 (IQR 1), P = 0.231.

3.5 Summary

The study population represented a younger patient group by a mean age of 1.4 years which is unlikely to represent a clinically meaningful difference between the two groups. A further difference was found in gender between the two groups. While the excluded patient group showed near gender-parity, the study population was two-thirds male. Given the database population has a

higher proportion of male patients who have undergone Nissen fundoplication, the study population is likely more representative of this group as a whole. A higher male representation may be expected given that the male incidence of complicated reflux disease (such as reflux oesophagitis) is more frequent compared to females.

No significant difference was found between the study population and excluded patient group based on absolute complication rate or complications stratified by time from surgery. Revisional surgery rates were also comparable between patient groups. It can therefore be postulated that outcome data from the study population should be a similar representation to that of the excluded patient group.

A significantly higher proportion of the excluded patient cohort underwent division of the short gastric vessels and a trend to higher operating times was found in this treatment group. This observation may be linked to longer operating times associated with division of the short gastric vessels.

CHAPTER 4 STUDY OF TWENTY YEAR CLINICAL OUTCOMES FOLLOWING LAPAROSCOPIC NISSEN FUNDOPLICATION

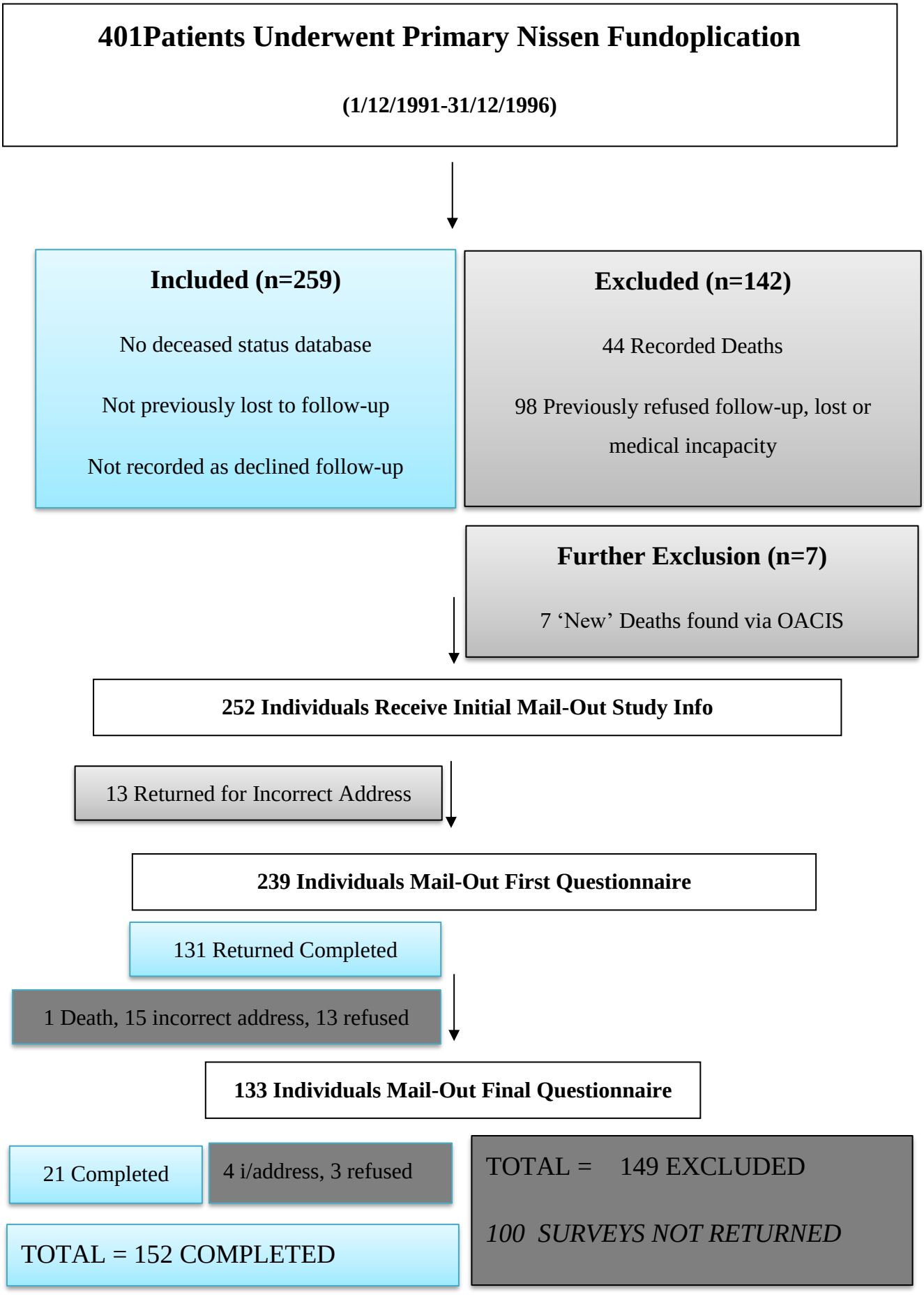
4.1 Study Group

A total of 401 patients were recorded on the surgical database as having undergone laparoscopic Nissen fundoplication surgery at twenty years or longer prior to study commencement. From within this group 149 patients with a minimum recording of demographic and operative data were not included in the study. A total of fifty-four patients were not included in the survey due to previous recording of deceased status on the surgical unit database or via OACIS demographic search. A further ninety-five individuals had previously refused, become mentally incapacitated or lost to follow-up prior to the study commencement. This resulted in a total study group number of 252 individuals who would subsequently be mailed study questionnaires.

4.2 Survey Response

Two-hundred and fifty-two patients were mailed surveys during the mail-out period. A completed survey on clinical outcomes was returned by mail by one hundred and forty-eight (58.7%). This was combined with a further four (1.6%) surveys which were returned by phone via study investigator, giving total completed questionnaires in one hundred and fifty-two individuals (60.3%). Patients who were allocated to initial mail-out but failed to return a completed questionnaire totalled one hundred, of which seventy-one (28.1%) did not return any correspondence. Thirteen patients (5.1%) refused study participation as recorded by response to the initial or subsequent study mail-out. Fifteen patients (5.9%) were unable to be contacted due to a change in address. A single patient (0.4%) within this group was notified to the research team as being recently deceased. Final allocation of patients in the study is shown in figure 4.1.

Figure 4-1 Study participant accrual.



4.3 Survey Respondents – Cohort Data

4.3.1 Demographics

Baseline demographic and clinical information of 152 (60.3%) patients who were mailed and returned clinical outcome surveys within the study period is shown in table 4.1.1. A total of 103 male (68%) and 49 female (32%) respondents were recorded. The mean and median age of respondents was 65 years (SD 11, IQR 7). Average age at fundoplication was 43.2 years (SD 12.3) with a median age of 45 years (IQR 14). Baseline body-mass index data was available for three-quarters of the group. Mean BMI was 26.7 kg/m^2 (SD 5.8) with median value 26.6 kg/m^2 (IQR 5.9).

4.3.2 Operative Technique

Primary procedure documented the presence of 70 hiatal herniae, although formal hiatal repair was recorded in a total of 103. The vast majority of fundoplications were completed without division of the short gastric vessels (131 patients, 86%). Open conversion was required in seven patients (5%). Mean procedure time for the cohort was 86.2 mins (SD 42.4) with a median time of 80 mins (IQR 36.5). The distribution was positively skewed (range 29-260 mins) with a significantly higher proportion of longer procedures completed in the first year of data collection compared to subsequent years (P = 0.001). The last procedure of three hours or greater duration was completed in April 1994. Nineteen percent of the patient group did not have a procedure time recorded in the surgical database.

4.3.3 Complications

In one-hundred and thirty (85%) patients no complications were recorded post procedure. Complication data was predominantly retrieved from a surgical unit database where the recording of low-grade complications (Clavien-Dindo classifications 1 and 2) was negligible. Hence complication data reported largely Clavien-Dindo classifications 3 and above. It is important to note that at the time laparoscopic Nissen fundoplication commenced the Clavien-Dindo system did not exist. Hence, complication data reported largely corresponds to more severe grades in the Clavien-Dindo classification system but this remains a retrospective attribution.

A total of twenty-two (13%) patients reported complications from the procedure for thirty-five documented procedure-associated adverse effects.

Intraoperative complications included three pneumothoraces, one episode of laryngospasm and a fall from an operating theatre table resulting in rib bruising.

Troublesome dysphagia within the early post-operative period was documented in eight (5%) patients. This delayed discharge in one patient without the need for intervention. In three patients, two early wrap revisions were required while the remaining patient improved with endoscopic dilatation alone. Gas-bloat syndrome was documented in two patients. One pulmonary embolism occurred post-operatively.

Para-oesophageal hernia was documented in eight patients (range 3 months - 11 years), resulting in revisional surgery in each. A total of five port-site hernia were documented as late procedure related complications (range 15-72 months) although the precise number who proceeded to surgery was unclear. Following the immediate post-operative period (30 days) and ten years follow-up, a total of fifteen complications were recorded (Para-oesophageal hernia seven patients, incisional herniae in five patients and troublesome dysphagia in three patients).

Greater than ten-year follow-up showed a further documented para-oesophageal hernia and port site hernia. In one patient, unspecified symptoms may be attributed to original surgery and were listed as a complication.

In total, revisional surgery was required in twenty-two (14%) patients, of which five (3%) were undertaken for symptoms in the immediate post-operative period (within one month of primary surgery). Dysphagia was implicated in six revisional surgeries.

Unspecified symptoms post fundoplication resulted in a further two early wrap revisions within three months of primary fundoplication.

4.3.4 Admission Data

Length of stay data was available for 134 patients within the group. Within a range of 1-12 days, the mean length of stay for the group was 4.0 days (SD 2.0) with a median 3 day admission (IQR 1.0). Similar to procedure times, length of stay over time showed positive skewness. Patients undergoing fundoplication during the first year of data collection had a longer length of stay compared to those in subsequent years of data collection (mean 4.7 days vs 3.6 days; P = 0.001).

4.3.5 Previous Trial Involvement

Fifty-eight individuals who responded to the current study had been involved in prior studies within the research group. A total of forty-two respondents were previously enrolled in the prospective double-blind randomised trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. These patients underwent fundoplication procedure between May 1994 and October 1995.

The remaining sixteen respondents were previously enrolled in the prospective randomised double-blind trial between laparoscopic Nissen fundoplication and anterior partial (180-degree) fundoplication. Participants in this trial underwent fundoplication surgery between December 1995

and April 1997.

4.3.6 Additional Investigations

Ninety-seven respondents (64%) reported additional investigations post fundoplication. The majority were endoscopy (gastroscopy) which were recorded in eighty-six (57%) respondents, followed by barium swallow study (twenty-four, 16%), oesophageal manometry (nine, 6%) and 24-hour pH monitoring (four, 3%). Three (2%) patients reported further investigations following fundoplication but did not state the type. Fifty-five (36%) patients did not report any further major investigational studies following their primary procedure.

Fifty-eight study respondents were enrolled in prior studies through the research group. The randomised trial of short-gastric division during laparoscopic Nissen fundoplication specified the following post-operative objective instigations: oesophageal manometry, 24-hour pH monitoring, barium swallow and gastric emptying study. The randomised trial of laparoscopic anterior partial 180-degree fundoplication versus laparoscopic Nissen fundoplication required post-operative gastroscopy in favour of barium swallow study, in addition to the above investigations.

Further, a total of twelve study respondents had a diagnosis of Barrett's oesophagus recorded. In this subgroup of patients follow-up gastroscopy during the study period would be a routine expectation.

Adjusting for the above planned investigations accounts for all reported post-operative barium swallow, oesophageal manometry and 24-hour pH monitoring studies in the study respondents. For gastroscopy, a total of fifty-eight respondents to the survey had this as a post-operative investigation which could not be accounted for by prior trial requirement or for routine Barrett's oesophagus surveillance.

Table 4-1 Baseline demographic data - study respondents, non-respondents and documented missing/deceased patients

		Study Respondents (n=152)		Non Respondents (n=100)		Missing and Deceased (n=149)		P	
		No.	%	No.	%	No.	%	SR/NR	SR/MD
Gender	Male	103	68	65	65	76	51	0.683	**0.003**
	Female	49	32	35	35	73	49		
Age (years)		**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**		
	Fundoplication	43.2 (12.3)	45 (18.5)	43.3 (13.3)	41 (19.7)	51.1 (16.0)	53 (26.5)	0.118	**0.001**
	Completion	64.6 (12.2)	65 (20.5)	64.3 (13.1)*	63 (18.0)*	67.6 (14.8)*	67 (24)*	0.075	0.657
Body Mass Index (kg/m^2)		**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**		
		26.7 (5.8)	26.6 (6)	26.4 (3.8)	26.7 (4.2)	28.5 (4.9)	28.5 (6.8)	0.516	0.078
	Missing Data		*38 (25%)*		*47 (47%)*		*85 (57%)*		

*Patients not previously recorded as deceased

Table 4-2 Operative data - study respondents, non-respondents and missing or deceased patients

	Study Respondents (n=152)		Non Respondents (n=100)		Missing and Deceased (n=149)		P	
Procedure Technique	**No.**	**%**	**No.**	**%**	**No.**	**%**	SR/NR	SR/MD
Hiatal Hernia / (formal repair)	70 / (103)	46 / (68)	44 / (67)	44 / (67)	85 / (110)	57 / (74)	0.796	**0.038**
							1.00	0.257
Short-Gastric Vessel Division	21	14	16	16	37	25	0.717	**0.019**
Open Conversion	7	5	9	9	18	12	0.191	**0.022**
Admission Data	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**		
Procedure time (mins)	86.2 (42.4)	80 (36.5)	98.9 (52.4)	80 (52.5)	95.7 (40.2)	85 (55)	0.225	**0.03**
Missing Data		*29 (19%)*		*19 (19%)*		*12 (8%)*		
Length of stay (days)	4.0 (2.0)	3 (1)	3.9 (2.1)	3 (1)	4.2 (2.6)	3 (2)	0.841	0.295
Missing Data		*18(12%)*		*17 (17%)*		*22 (15%)*		

Table 4-3 Complication Data and Revisional Procedures - study respondents, non-respondents and missing or deceased patients

	Study Respondents (n=152)		Non Respondents (n=100)		Missing and Deceased (n=149)		P	
Complications	No.	%	No.	%	No.	%	SR/NR	SR/MD
Intraoperative	5	3	5	5	4	3	0.521	1.00
Early (< 31 days)	14	9	7	7	9	6	0.644	0.302
Delayed (31 days - 10 years	15	10	7	7	18	12	0.5	0.595
Long Term (> 10 years)	1	1	2 (incomplete)	NA	NA	NA	NA	NA
Total By Patient	22	14	15	15	31	21	1.00	0.421
Revisional Surgery								
Early (< 31 days)	5	3	3	3	10	7	1.00	**0.043**
Delayed (31 days – 10 years)	14	9	11	11	19	13	0.671	0.697
Late (10 years+)	6	4	NA	NA	NA	NA	NA	NA
ALL Revisions	25	16	14	14	29	19	1.00	0.354

Table 4-4 Investigations post fundoplication - study respondents only

	No.	%
Endoscopy (gastroscopy)	86	57
Investigation without prior trial requirement or Barrett's oesophagus diagnosis	58	38
Barium Swallow	24	16
Investigation without enrolment SGVD trial	0* (18)	0
Oesophageal Manometry	9	6
Investigation without prior trial requirement	0* (49)	0
24 pH Monitoring	4	3
Investigation without prior trial requirement	0* (54)	0
New Investigation not specified	3	2
No further investigations	56	37
***All investigations accounted for by previous trial requirement. Figure in parenthesis represents additional number of each post-operative investigation required if all patients had completed all required objective follow-up investigations as specified per previous study protocol(s). This**		

number may indicate the estimated number of under-report for each investigation.

4.4 Study Respondents – Clinical Outcomes

For study participants completing the questionnaire, mean clinical follow-up of 265 months (SD 17.8), median 269 (IQR 34.5) for 152 patients was recorded.

4.4.1 Heartburn Control

The study investigated heartburn as a symptom via a visual-analogue score between values of 0-10, where a score of ten implies a severe, intractable symptom while zero is freedom from heartburn as an individual symptom. The study respondents reported a mean visual-analogue score (range 0-10) for heartburn of 1.8 (SD 2.5). This was a significant reduction from the pre-operative average of 7.4 (SD 3.0), P = 0.001.

The frequency of heartburn was reported by respondents via selection of one of six options ranging from the symptom as an ‘every meal’ experience to ‘never’. The most common report was ‘occasional’ heartburn (sixty-six respondents, 43%), followed by ‘never’ (sixty-two, 41%). Five percent of patients experienced daily and weekly symptomatic heartburn (eight patients). Monthly heartburn was reported in four patients (3%). A single patient reported heartburn with every meal. In three (2%) respondents the frequency of heartburn was unspecified.

4.4.2 Symptomatic Regurgitation

The symptom of regurgitation was recorded using the same visual-analogue score and frequency options as per heartburn. The study respondents reported a mean visual-analogue score (range 0-10) for regurgitation of 1.3 (SD 2.2).

Eighty-five individuals (56%) reported the frequency of regurgitation as an individual symptom as ‘never’. Occasional regurgitation was reported in forty-eight respondents (32%). Eight patients (5%) reported regurgitation as a weekly symptom. Three percent (five patients) experienced daily and monthly regurgitation. No patient reported regurgitation with every meal. In a single patient the frequency of regurgitation was not specified.

4.4.3 Dysphagia

Dysphagia as a global symptom (any severity, any frequency) was reported in eighty-three patients (55%). This was a higher report of any dysphagia as a symptom compared to pre-operative data

for the cohort (55% vs 36%), albeit without reaching statistical significance and limited by thirteen percent of the cohort not recording any baseline dysphagia information. In addition, dysphagia as a symptom while more numerously reported, was at a lower average severity compared to pre-operative scores.

Dysphagia as an individual symptom to solids and liquids was recorded using a visual-analogue score as per heartburn and regurgitation. The mean visual-analogue score for dysphagia (range 0-10) was 1.9 (SD 2.3) for solids which was lower than preoperative average score (2.2, SD 3.4), P = 0.381. Mean dysphagia score with liquids was 1.1 (SD 2.0) compared to preoperative 1.3 (SD 2.8), P = 0.425.

Sixty-eight (45%) of respondents reported occasional dysphagia. This was followed by twelve respondents (8%) who experienced weekly dysphagia. Monthly and daily dysphagia was recorded by six (4%) and five (3%) patients, respectively. No patient reported dysphagia with every meal and forty percent (sixty-one) of respondents specified never experiencing dysphagia by symptom frequency.

Table 4-5 Clinical outcomes of study respondents at mean follow-up 265 months – Heartburn and Regurgitation

	20 Year Follow-up		Preoperative		
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**P**
Heartburn (VA 0-10)	1.8 (2.5)	1 (2.5)	7.4 (3.0)	8 (5)	**0.001**
	Missing Values 1		Missing Values 10		

	EVERY MEAL	DAILY	WEEKLY	MONTHLY	OCCASIONALLY	NEVER	NOT STATED
Heartburn Frequency	1 (1%)	8 (5%)	8 (5%)	4 (3%)	66 (43%)	62 (41%)	3 (2%)

	20 Year Follow-up		Preoperative		
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**P**
Regurgitation (VA 0-10)	1.3 (2.2)	0 (2)	NA	NA	NA
	Missing Values 1		Missing Values NA		

	EVERY MEAL	DAILY	WEEKLY	MONTHLY	OCCASIONALLY	NEVER	NOT STATED
Regurgitation Frequency	0 (0%)	5 (3%)	8 (5%)	5 (3%)	48 (32%)	85 (56%)	1 (1%)

Table 4-6 Clinical outcomes study respondents at mean follow-up 264 months – Dysphagia

	20 Year Follow-up		Preoperative		
Dysphagia YES/NO	**YES**	**NO**	**YES**	**NO**	**p**
	83 (55%)	68 (45%)	55 (42%)	77 (58%)	0.253
		Missing 1		Missing 20	
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**p**
Dysphagia Solids	1.9 (2.3)	1 (3)	2.2 (3.4)	0 (5)	0.381
		Missing 4		Missing 22	
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**p**
Dysphagia Liquids	1.1 (2.0)	0 (1)	1.3 (2.8)	0 (0)	0.425
		Missing 1		Missing 7	

	EVERY MEAL	DAILY	WEEKLY	MONTHLY	OCCASIONALLY	NEVER	NOT STATED
Dysphagia Frequency	0 (0%)	5 (3%)	12 (8%)	6 (4%)	68 (45%)	61 (40%)	0 (0%)

4.4.4 Other and Atypical Symptoms

The most common atypical symptom was increased flatus (53%, eighty-one patients). Epigastric bloat was also experienced in around one in two respondents (51%, seventy-eight). However, the inability to relieve bloat was only reported in thirty-four patients (22%). Sixty-two patients reported some degree of postprandial fullness (41%) with the inability to belch in fifty-nine, 39%. Epigastric pain was experienced by twenty-four percent of patients (thirty-seven). Shortness of breath was documented in twenty-three percent of patients (thirty-five). Other respiratory symptoms such as nocturnal cough and nocturnal wheeze were less common, 17% and 8%, respectively. Non-specific gastrointestinal symptoms of diarrhoea, nausea and vomiting were reported in a minority of respondents, 18%, 17% and 4%, respectively. Chest pain was reported by twenty-five patients (16%). Odynophagia and nocturnal choking attacks were relatively less common in 5% (eight) and 4% (six) of respondents.

Sixteen percent (twenty-four) or respondents reported freedom from the above symptoms.

4.4.5 Most troublesome symptom

Dysphagia was the most frequently reported troublesome symptom (twenty-one patients, 14%). Epigastric bloat was the second most frequently-reported troublesome symptom (thirteen patients, 9%), closely followed by heartburn (twelve patients, 8%). Five patients (3%) reported flatus as the most troublesome symptom. Each of the remaining atypical symptoms were infrequently reported as the ‘worst’ symptom by a minority of study respondents. A large proportion of patients declined to specify a response to this question (seventy-one patients, 47%). Further, twenty-four patients (16%) stated they were symptom free and could not therefore provide an answer in this field.

Table 4-7 Clinical outcomes: study respondents – Atypical and Other Symptoms

	No.	%
Increased Flatus	81	53
Epigastric Bloat	78	51
Post-prandial Fullness	62	41
Inability to belch	59	39
Epigastric Pain	37	24
Inability to Relieve Bloat	35	23
Shortness of Breath	35	23
Diarrhoea	28	18
Nausea	26	17
Nocturnal Cough	26	17
Chest Pain	25	16
Nocturnal Wheeze	12	8
Odynophagia	8	5
Nocturnal Choking Attacks	6	4
Vomiting	6	4
Atypical/Other Symptom Free	*24*	*16*

Table 4-8 Clinical outcomes: study respondents – Most Troublesome Symptom

	No.	%
Not Stated / Missing	71	47
None predominate	24	16
Dysphagia	21	14
Heartburn	12	8
Epigastric Bloat	5	3
Increased Flatus	5	3
Chest Pain	2	2
Diarrhoea	2	2
Epigastric Pain	2	2
Post-prandial Fullness	2	2
Regurgitation	2	2
Inability to belch	1	1
Inability to Relieve Bloat	1	1
Nausea	1	1
Nocturnal Cough	1	1

4.4.6 Antireflux Medications

The proton-pump inhibitor class were the most common antireflux medication recorded (fifty-nine patients, 39%). Within this group, esomeprazole was the commonest (thirty), followed by pantoprazole (twenty-two), omeprazole (four) and rabeprazole (three). Five patients were taking the H2-receptor antagonist ranitidine. Twenty patients reported some antacid use, of which Mylanta® and Gaviscon® were the most popular (twelve, 8% and five, 3%). A single patient was taking the muco-protectant agent sucralfate.

Table 4-9 Clinical outcomes: study respondents – Antireflux Medication Use

Pharmacological Group	Medication	No.	%
Proton Pump Inhibitor	Esomeprazole	30	20
	Omeprazole	4	3
	Pantoprazole	22	14
	Rabeprazole	3	2
	ALL PPI	**59**	**39**
H2-Receptor Antagonist	Ranitidine	5	3
	ALL H2 Receptor Antagonists	**5**	**3**
Antacids	Gaviscon®	5	3
	Mylanta®	12	8
	Rennie®	5	3
	Antacid (other)	1	1
	ALL Antacids	**23**	**15**
Mucoprotectant	**Sucralfate**	**1**	**1**

4.4.7 Surgery Outcome

The overall outcome of surgery was investigated using patient responses to multiple survey fields. These were an overall description of surgical outcome within four brief descriptions (excellent, good, fair or poor), a modified-Visick scale, visual-analogue rating scale (range 0-10) and a direct question as to whether the respondent would undergo the fundoplication surgery again.

A large majority of respondents selected the outcome of surgery as ‘excellent’ or ‘good’ in seventy (46%) and sixty-one (40%) patients, respectively. A total of sixteen respondents (10%) rated it as ‘fair’, with only five cases (3%) selecting ‘poor’.

The modified-Visick scale used a scoring range 1-5, whereby:

1. A patient who is symptom free
2. A patient who has mild symptoms controlled by simple care
3. A patient who has moderate symptoms which are not controlled by simple care but which do not interfere with social life or work
4. A patient who has moderate symptoms interfering with social life or work
5. A patient whose symptoms are as bad or worse following surgery

By the above modified-Visick parameters, a total of forty-five patients (30%) were symptom-free. The majority of patients (eighty-seven, 57%) selected Visick 2 indicating mild symptoms that are controlled by simple care. For those individuals with moderate symptoms, fourteen (9%) deemed these to not interfere with social life or work. In two patients, moderate symptoms interfered with social life or work. A further two patients deemed their symptoms to be as bad or worse following fundoplication. Two individuals omitted to make a selection in the modified-Visick field

Mean visual-analogue score (range 0-10) for satisfaction of surgery was 8.4 (SD 2.4).

The final clinical outcome question posed the question: ‘Having gone through this operation and knowing now what is involved, would you have made the same decision to have the same operation for same problem (In other words, do you think you made the correct decision when you agree to have the operation)? In answer to this question, ninety-one percent (129 patients) of respondents elected yes (twelve ‘no’ responses and eleven failed to provide an answer).

Table 4-10 Clinical outcomes: study respondents – Overall Satisfaction

Patient Appraisal Surgery Outcome		**EXCELLENT**	**GOOD**	**FAIR**	**POOR**	**NOT STATED**	
	No.	70	61	16	5	0	
	%	46	40	10	3	0	
		1	**2**	**3**	**4**	**5**	**NOT STATED**
Modified-Visick	No.	45	87	14	2	2	2
	%	30	58	9	1	1	1
		Mean (SD)		**Median (IQR)**			
Satisfaction VA 0-10		8.5 (2.3)		9 (2)			

Missing 1

		YES	NO	No valid response
Would have surgery again	**No.**	129	12	11
	%	85	8	7

4.6 Internal Validity

To verify consistency of data recorded in the surgical database against patient responses to the current questionnaire, a comparison was made between patient evaluation of the symptoms of heartburn and dysphagia, as well as the modified-Visick score and overall satisfaction of surgery scores between the two datasets. The most recent recording in the database for each parameter of each respondent was taken for comparison with the current questionnaire response.

4.6.1 Patient Symptoms

Visual-analogue (0-10) scoring for heartburn as a symptom returned a mean value of 1.8 (SD 2.5) in the current study. Using the last data point recorded in the surgical database for each study respondent, the mean heartburn visual-analogue score (0-10) was 1.8 (SD 2.8) P = 0.586.

The current study returned a mean dysphagia score for solids of 1.9 (SD 2.3). The database-derived mean value for dysphagia with solids was 2.4 (SD 2.6), P = 0.144. Dysphagia with liquids returned a mean value of 1.1 (SD 2.0) using the current questionnaire and 1.3 (SD 2.2) using database-derived scores, P = 0.211.

4.6.2 Patient Satisfaction with Surgery

The study respondents at completion of follow-up returned a mean visual-analogue (0-10) score for overall satisfaction of surgery of 8.5 (SD 2.3). The mean derived from the last database value for the cohort was 8.5 (SD 1.9), P = 0.454.

A modified-Visick score of 1 or 2 was recorded in 132 respondents (88%) in the current study. Database searching retrieved 121 patients (80%) who reported a modified-Visick score of 1 or 2 in their last follow-up interval, p=0.761. Modified-Visick score of 3, 4 or 5 from the last retrieved follow-up in the surgical database was recorded in seventeen (11%), five (3%) and three (2%) patients, respectively. A database recording in this field was unavailable in six patients. Table 4-11 shows stratification by modified-Visick score for each method of follow-up.

4.6.3 Summary

No statistically-significant difference was found between each parameter in the validity verification.

Table 4-11 Modified-Visick scores derived from current study and database search

Modified-Visick		1	2	3	4	5	*NOT STATED*
Current Study	**No.**	45	87	14	2	2	2
	%	30	58	9	1	1	1
Last Database Recording	**No.**	47	74	17	5	3	6
	%	31	49	11	3	2	4

4.7 Survey Non-Respondents – Cohort Data

A total of one-hundred (40%) patients who were mailed clinical outcome surveys did not return completed surveys within the study period. Following mailing of initial invitation to participate information leaflets to two-hundred and fifty-two individuals in July 2016, thirteen were initially returned for incorrect address. The first survey mail-out was completed in August 2016 and a further fifteen surveys were returned for incorrect address. Thirteen patients responded that they were refusing to participate in the current study while a single death was notified to the study group. Following final survey mail-out in September 2016, a final four surveys were returned for incorrect address while another three patients refused to participate in the study. No response was received from fifty-one patients who were mailed study materials.

4.7.1 Demographics

Baseline demographic and clinical information is shown in table 4-1. A total of 65 male (65%) and 35 (35%) female respondents were recorded. The mean and median age of the non-respondents was 64.3 and 63 years, respectively (SD 13.1, IQR 18.0). The mean and median body-mass index for the group was 26.4 kg/m^2 and 26.7 kg/m^2, respectively (SD 3.8, IQR 4.2). However, baseline BMI data was not available for just under half the cohort. No statistically-significant variation in either gender or BMI was found between this cohort and that of the study respondents.

4.7.2 Operative Technique

Primary procedure documented 44 hiatal herniae, although formal repair was recorded in 67 patients. Division of the short gastric vessels occurred in a minority of the cohort (sixteen patients, 16%). Open conversion was required in nine patients (9%). Mean procedure time was 98.9 minutes (SD 52.4) with a median of 80 minutes (IQR 52.5). In just under one-fifth of patients a procedure time was not recorded. A significantly higher proportion of procedures of 180 minutes or longer were completed within the first 18 months of database activity which may reflect a learning curve bias. No statistically-significant variation was found between the study respondents and non-respondents based on the above variables in operative technique.

4.7.3 Complications

Eighty-five patients (85%) reported no significant operative complications post procedure. A total of fifteen patients experienced either a Clavien-Dindo grade 3 or 4 complication, which was marginally higher than for the study respondent group (15% vs. 14%), without reaching statistical

significance (p=0.583). Five intraoperative complications were recorded including two iatrogenic gastric perforations, left hepatic vein injury, unspecified liver laceration and bilateral pneumothoraces.

Troublesome dysphagia within the early post-operative period was documented in two (2%) patients, requiring endoscopic revision in one patient and surgical revision in another. Para-oesophageal herniae accounted for significant symptoms within one week following fundoplication in three patients and all required surgical intervention. Unspecified symptoms in two patients were confirmed in two patients and required operative intervention early in the post-operative course.

A total of fourteen patients underwent revisional surgery. Symptomatic para-oesophageal herniae accounted for five procedures. Dysphagia was the predominant symptom in three revisions. Symptomatic return of GORD symptoms accounted for one revision. Unspecified symptoms post fundoplication resulted in a total of five further wrap revisions. One patient experienced an episode of gastric outlet obstruction at ten months post fundoplication which required surgical intervention and wrap revision. A total of three revisions (3%) were required within the first month of surgery. The remaining eleven revisional procedures were completed following one month and within ten years post-surgery.

4.7.4 Admission Data

The one-hundred patients had a mean length of hospital stay of 3.9 days (SD 2.1). The median length of stay was three days (IQR 1) within a range of 1-10 days. No significant difference was found in length of stay between study respondents and non-respondents.

4.8 Study Non-Respondents – Clinical Outcomes

Mean clinical follow-up was 211 months (SD 40), median 229 months (IQR 60) for 100 patients who refused or were unable to be followed up using the current questionnaire.

4.8.1 Heartburn Control

The surgical database contained visual-analogue scores (0-10) for heartburn at variable follow-up intervals between baseline and twenty years. The most recent recorded result for heartburn was taken for all non-respondents. This resulted in a mean visual-analogue score (range 0-10) for heartburn of 1.5 (SD 2.5) and median 0 (IQR 2). This represented a statistically-significant reduction from baseline heartburn score (1.5 vs 7.5, $P < 0.001$). Table 4-12 shows tabulated

symptom scores for this individual cohort. No statistically-significant difference was found in visual-analogue heartburn scores between study respondent and non-respondent groups.

4.8.2 Dysphagia

Symptomatic dysphagia was reported in fifty-two patients (54%). Similar to the current study questionnaire, dysphagia as an individual symptom to both solids and liquids had been recorded using a visual-analogue score. The mean visual-analogue score for dysphagia (range 0-10) was 2.2 (SD 2.8) for solids and 1.1 (SD 2.1) for liquids. Baseline preoperative dysphagia scores were similar for both solids (2.1, SD 3.4) and liquids (1.5, SD 3.0). A significantly higher report of any dysphagia as as a symptom was found post-operatively compared to baseline (54% vs 35%, P = 0.01). However, a significant proportion of preoperative dysphagia scores were not recorded in the database (19 patients). No statistically-significant difference was found in visual-analogue dysphagia scores for liquids or solids between study respondents and non-respondents.

Table 4-12 Clinical outcomes of non-respondents at mean follow-up 211 months – Heartburn and Dysphagia

	Last Recorded Follow-up		Preoperative		
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**P**
Heartburn (VA 0-10)	1.5 (2.5)	0 (2)	7.5 (3.4)	9 (4)	**0.001**
		Missing Values 1		Missing Values 15	
Dysphagia YES/NO	**YES**	**NO**	**YES****	**NO**	**P**
	52 (54%)	45 (46%)	28 (35%)	54 (65%)	**0.01**
		Missing 2		Missing 19	
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**P**
Dysphagia Solids	2.2 (2.8)	1 (4)	2.1 (3.4)	0 (4)	0.155
		Missing 2		Missing 19	
	Mean (SD)	**Median (IQR)**	**Mean (SD)****	**Median (IQR)**	**P**
Dysphagia Liquids	1.1 (2.1)	0 (1.2)	1.5 (3.0)	0 (2)	0.967
		Missing 2		Missing 19	

4.8.3 Antireflux Medications

Antireflux medication use was reported in twenty-seven patients (27%). Proton-pump inhibitors were the most commonly prescribed with a total of twenty-two (22%) patients taking one of the medication group. Specifically this was esomeprazole in nine patients (9%), omeprazole (five, 5%), pantoprazole (four, 4%), rabeprazole (three, 3%) and a single patient was taking lansoprazole. One patient was taking ranitidine at most recent follow-up. Seven patients reported some use of antacid medication.

Table 4-13 Study non-respondents – Antireflux Medication Use

Pharmacological Group	Medication	No.	%
Proton Pump Inhibitor	Esomeprazole	9	9
	Lansoprazole	1	1
	Omeprazole	5	5
	Pantoprazole	4	4
	Rabeprazole	3	3
	ALL PPI	**22**	**22**
Antacids	Various (not specified)	7	7

4.8.4 Surgery Outcome

The overall outcome of surgery was previously recorded using the same survey fields to that of the current study, namely modified-Visick scale, visual-analogue rating scale (range 0-10) and direct question as to whether the respondent would undergo surgery again.

By the previously stated modified-Visick parameters, a total of twenty-nine patients (39%) were symptom-free. Thirty patients (40%) selected Visick 2. For those individuals with moderate symptoms, nine (12%) deemed these to not interfere with social life or work. In four patients (5%), moderate symptoms interfered with social life or work. Only three patients (4%) deemed their symptoms to be as bad or worse following fundoplication. The modified-Visick database field was blank for twenty-five individuals.

Mean visual-analogue score (range 0-10) for satisfaction of surgery was 8.3 (SD 2.5); median 9 (IQR 2.1). This was similar to the VA score from the responder group (mean 8.5 (SD 2.3); median 9 (2), P = 0.454).

The final clinical outcome question posed the question: ‘Having gone through this operation and knowing now what is involved, would you have made the same decision to have the same operation for same problem (In other words, do you think you made the correct decision when you agree to have the operation)?

For the aforementioned question eighty-five percent (81) of respondents were in the affirmative (marginally less than the respondent group at 91%). Fourteen patients (15%) responded in the negative, while five individuals did not have a recorded response to the question on the database.

Table 4-14 Study non-respondents – Overall Surgery Outcome

		1	2	3	4	5	NOT RECORDED
Modified-Visick	**No.**	29	30	9	4	3	25
	%	39	40	12	5	4	

		Mean (SD)	**Median (IQR)**
Satisfaction VA 0-10		8.3 (2.5)	9 (2.1)

Missing 2

		YES	NO	No valid answer
Would have surgery again	**No.**	81	14	5
	%	81	14	5

4.9 Patients not enrolled in current study – Cohort Data

A significant number of patients were recorded in the database as having undergone laparoscopic Nissen fundoplication at twenty years or earlier from study commencement but were unable to be included in the questionnaire due to either previously being listed as deceased, unwilling to be involved in future surveys or previously lost to follow-up. These totalled 149 patients and each had a minimum recording of demographic, operative and follow-up to permit inclusion in the analysis. A total of forty-four deaths had been previously recorded in this cohort, while ninety-eight patients had previously refused or been lost to follow-up, or been rendered mentally or physically incapacitated to future study participation. Prior to survey mail-out, cross-referencing for deceased notifications using the OACIS application found a further seven deaths from within the global fundoplication cohort. Mean clinical follow-up for patient group not enrolled in the current study (n=149) was 118 months (SD 66), median 132 months (IQR 100).

4.9.1 Demographics

Baseline demographic information for this group is listed in table 4-1. Data from a total of 76 male (51%) and 73 (49%) female patients were collated. For those patients not previously recorded as deceased, the mean age of this group was 67.6 years (SD 14.8), median age 67 years (IQR 24). This cohort was significantly older at operation (51.1 vs 45.0 years, P = 0.001) and with a greater proportion of females (49% vs 32%, P = 0.003) than the reference study population. This difference in average age between the two groups diminished over time when comparison was made of surviving patient age at the end of follow-up. Body-mass index data was only available in a minority of patients with a mean of 28.5 kg/m^2 (SD 4.9).

4.9.2 Operative Technique

A total of 85 patients were recorded as having a hiatal hernia but formal repair was recorded in 110 (74%). Short-gastric vessels were divided in thirty-seven patients (25%). In comparison, the study respondent population had a lower rate of short-gastric vessel division (14%), P = 0.019. Open conversion was required in eighteen patients (12%) which was also a significantly higher proportion than the reference study cohort (4%), P = 0.022. Mean procedure times averaged 95.7 minutes (SD 40.2) for the group which were longer than the study respondents by nine and a half minutes (86.2 minutes; SD 42.4), P = 0.037.

4.9.3 Complications

A complication following primary fundoplication surgery was recorded in thirty-one patients (21%). A single mortality was attributed to the primary surgery. This patient was found to have an ischaemic wrap when returned to theatre at day 5. Following multiple laparotomies, there was progression of mesenteric ischaemia and the patient died at day 30 from complications of liver failure.

Intraoperative complications were documented in four patients. These were two aspiration events requiring admission to intensive-care unit care in the immediate post-operative period, one pneumothorax and one bleeding event. Intraoperative bleeding from a liver laceration occurred in one patient, while a further patient experienced bleeding within the immediate recovery period requiring return to theatre to control haemorrhage from a short-gastric vessel.

Nine complications were reported within thirty days of primary surgery. A further patient experienced a food bolus obstruction at day 21 post surgery that did not require initial surgical intervention but later proceeded to revisional surgery secondary to hiatal stenosis. Venous thromboembolic events accounted for two early complications from one pulmonary embolism and a further deep venous thrombosis. A single patient had intractable odynophagia and abdominal pain following open-converted fundoplication which was investigated with laparascopy without wrap revision.

Troublesome dysphagia within three months of fundoplication was recorded in five patients, requiring surgical intervention in three cases.

Late complications (1 month-10 years post-surgery) were documented in eighteen patients (12%). The majority were from para-oesophageal herniae (nine) and incisional herniae (five). Dysphagia was the predominant symptom requiring further investigation and surgical management in two patients. Poor control of reflux symtpoms and other non-specific gastrointestinal symptoms were documented in two patients and resulted in revisional surgery. Hiatal stenosis was documented in another patient who underwent revisional surgery at 7 months for unspecified symptoms while another patient underwent refashioning of the fundoplication secondary to a bilobed stomach. Incisional herniae were recorded in three patients following open-conversion fundoplication with the two remaining hernia from a laparoscopic port sites.

Revisional fundoplication surgery was required in a total of twenty-five patients (17%). Para-oesophageal herniae and dysphagia were the primary indications in nine and ten wrap revisions, respectively. Recurrent heartburn accounted for two revisions. Non-specific recurrent reflux symptoms were cited in the remaining four fundoplication revisions.

4.9.4 Admission Data

No significant difference in average length of stay was found between the study groups. Patients who were previously missing or deceased had a mean length of stay of 4.2 days (SD 2.6).

4.10 Patients Not Enrolled in Current Study – Clinical Outcomes

4.10.1 Heartburn Control

The most recent recorded visual-analogue result for heartburn was taken from the database for all patients within the group. This resulted in a mean visual-analogue score (range 0-10) for heartburn of 1.6 (SD 2.9) and median 0 (IQR 2). This represented a statistically-significant reduction from baseline heartburn score (1.6 vs 7.5, $P < 0.001$). Table.4-15 shows tabulated symptom scores for this individual cohort.

4.10.2 Dysphagia

Symptomatic dysphagia was reported in eighty-two patients (55%). This represented a significantly higher report than baseline reported dysphagia (44%), p 0.015. The mean visual-analogue score for dysphagia (range 0-10) was 2.9 (SD 3.2) for solids and 1.7 (SD 2.8) for liquids. Compared to the preoperative dysphagia values, no significant difference was found for either solids (2.6, SD 3.6) or liquids (1.8, SD 3.3).

Table 4-15 Clinical outcomes patients not in current study at mean follow-up 119 months – Heartburn and Dysphagia

	Last Recorded follow-up		Preoperative		
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**P**
Heartburn (VA 0-10)	1.6 (2.9)	0 (2)	7.5 (3.3)	9 (5)	**<0.0001**
		Missing Values 3		Missing Values 14	
Dysphagia YES/NO	**YES**	**NO**	**YES**	**NO**	**P**
	82 (59%)	57 (41%)	58 (44%)	74 (56%)	**0.015**
		Missing 10		Missing Values 17	
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**P**
Dysphagia Solids	2.9 (3.2)	2 (5)	2.6 (3.6)	0 (5)	0.168
		Missing 10		Missing Values 16	
	Mean (SD)	**Median (IQR)**	**Mean (SD)****	**Median (IQR)**	**P**
Dysphagia Liquids	1.7 (2.8)	0 (3)	1.8 (3.3)	0 (2.0)	0.554
		Missing 9		Missing Values 16	

4.10.3 Antireflux Medications

Antireflux medication use was recorded in the database for thirty-three patients (22%) within the group. Proton-pump inhibitors were prescribed in twenty-two (15%). Esomeprazole and omeprazole were taken by nine patients each (6%), pantoprazole (three, 2%), and a single patient was taking lansoprazole. Two patients (1%) were recorded as taking ranitidine at last follow-up. Antacid medication were taken by five patients (3%). In four patients (3%) antireflux medication was being taken at most recent follow-up interval but further information was not disclosed to the study team.

Table 4-16 Excluded patients – Antireflux Medication Use

Pharmacological Group	Medication	No.	%
Proton Pump Inhibitor	Esomeprazole	9	6
	Lansoprazole	1	1
	Omeprazole	9	6
	Pantoprazole	3	2
	ALL PPI	**22**	**15**
H2-Receptor Antagonist	Ranitidine	2	1
Antacids	Various (not specified)	5	3

4.10.4 Surgery Outcome

As for the other study groups, the overall outcome of surgery was previously recorded using modified-Visick scale, visual-analogue rating scale (range 0-10) and direct question as to whether the respondent would undergo surgery again.

The modified-Visick scale was of limited utility to this patient group owing to just over two-thirds of patients not having a recorded selection for this field within the database (101 patients, 68%). Thirteen patients (9%) were symptom-free. Twenty-five patients (17%) nominated mild symptoms that were controlled by simple care. Five patients categorised moderate symptoms, three (2%) deemed these to not interfere with social life or work. In two patients (1%), moderate symptoms interfered with social life or work. Five patients (3%) deemed their symptoms to be as bad or worse following fundoplication.

Mean visual-analogue score (range 0-10) for satisfaction of surgery was 7.3 (SD 3.4); median 9 (IQR 4) for the patient group.

The final clinical outcome question posed the question: ‘Having gone through this operation and knowing now what is involved, would you have made the same decision to have the same operation for same problem (In other words, do you think you made the correct decision when you agree to have the operation)?

In response to the aforementioned question 114 patients (81%) responded in the affirmative. Twenty-six patients (19%) were recorded as not being willing to undergo the surgery again. Four individuals did not select a valid response in this question field.

Table 4-17 Study non-respondents – Overall Surgery Outcome

		1	2	3	4	5	NOT RECORDED
Modified-Visick	**No.**	13	25	3	2	5	**101**
	%	9	17	2	1	3	**68**

		Mean (SD)	**Median (IQR)**
Satisfaction VA 0-10		7.3 (3.4)	9 (4)

Missing 4

		YES	NO	Invalid Response
Would have surgery again	**No.**	114	26	4
	%	81	19	

4.11 Discussion – Clinical Outcomes

The clinical outcomes of 152 patients who returned completed surveys at a mean follow up of 264 months post laparoscopic Nissen fundoplication represents the longest interval of outcome data recorded. Luostarinen and colleagues retrospective analysis of 25 patients (median follow-up 20 years) post open Nissen fundoplication and Robinson et al prospective case-series of 51 patients (median 19.7 years) post laparoscopic Nissen fundoplication are other ultra-long term follow-up studies in the area.[26, 114] Both these earlier studies were limited by small patient numbers and in the case of the latter, a very low rate of follow-up completion. The current study showed a survey response of 60% whose responses are more likely to be representative of the study population than similar studies with lower rates of follow-up completion. All three studies show high rates (>90%) of heartburn control at ultra-long term follow-up. Heartburn control was consistently improved from baseline levels for all patient groups in the current study. At the longest follow-up interval of 22 years, mean visual-analogue values for heartburn remained low for study respondents.

Outcome data from study survey respondents did not vary significantly from that of both survey non-respondents and patients excluded from the study. Specifically the parameters of heartburn control and symptom report such as dysphagia remained comparable between groups. This suggests the outcomes for the respondents is indicative of patients at long-term. A limitation of this direct comparison is the disparity in follow-up intervals between each patient group as mean follow-up for study respondents was greater than double that the comparison groups.

The significant use of proton-pump inhibitor medication within the study group places a question over the durability of the technique. Given that a majority of the study population underwent surgery for medication-refractory GORD after therapy with omeprazole, the achievement of heartburn control at long follow-up with or without medical therapy is notable. In addition, the increase in uptake of PPI medication over time post antireflux surgery reflects previous studies

both locally and abroad demonstrating this trend. Further, numerous publications have shown a majority of patients are not taking antireflux medication for recurrence of heartburn symptoms but are instead being treated by general practitioners for a variety of non-specific gastrointestinal symptoms.

The tolerability of laparoscopic Nissen fundoplication at long-term follow-up remains high. This was evidenced by low visual-analogue symptom scores in each patient group. This included dysphagia, a symptom which has been cited as a limitation of the technique. While the study reported absolute rates of dysphagia at 50-55%, only a minority of patients (<5%) reported daily or more frequent symptoms. Hence dysphagia experienced at any point post procedure and at any severity or frequency remain a common report, the incidence of troublesome dysphagia remained low.

A clear limitation of the study remains a lack of objective investigations. Without gastroscopy, pH studies or manometry analysis, the burden of incomplete fundoplications or objective-confirmed GORD remains unknown in this study cohort. As stated previously, significant barriers are encountered when applying objective testing following antireflux surgery to patients at long follow-up periods and particularly when patients remain asymptomatic. These include but are not limited to patient reluctance for invasive tests which may be uncomfortable and limitations on local health care resources. Further, the utility of these objective investigations has been questioned owing limited correlation to patient reflux symptoms. [7]

4.12 Conclusions – Clinical Outcomes

Laparoscopic Nissen fundoplication offers durable efficacy at up to 22 years follow-up for medication-refractory gastro-oesophageal reflux disease. The report of symptoms such as dysphagia is common but only a minority experience daily or troublesome symptoms. Satisfaction with surgery outcome remains high at extended follow-up intervals.

CHAPTER 5 QUALITY OF LIFE OUTCOMES AT TWENTY YEARS FOLLOW-UP FOLLOWING LAPAROSCOPIC NISSEN FUNDOPLICATION

5.1 Introduction

During the 1990s numerous treatment centres adopted the laparoscopic Nissen fundoplication technique as a standard treatment modality for medication-refractory gastro-oesophageal reflux disease. The procedure was shown in multiple studies to offer effective reflux control but this effect may be partly offset by troublesome side effects experienced in a minority of patients. [74, 75] Clinical outcomes have been recorded in the form of patient reported measures based on symptom scoring systems which aim to standardise the frequency and severity of GORD and treatment-associated symptoms. Early patient symptom reports on quality of life outcomes have shown improvement following antireflux surgery and specifically with laparoscopic Nissen fundoplication. [92, 128] However, strong associations between patient-reported GORD symptoms and general quality of life indicators remain elusive in many studies. Further, the effect of laparoscopic Nissen fundoplication on long-term quality of life measures beyond ten years follow-up is largely lacking.

A range of quality of life instruments specific to gastrointestinal symptoms have been developed. In a number of these tools, reflux-related symptoms form a component of an overall gastrointestinal global measure. Among these, the GIQLI (Gastrointestinal quality of life) instrument developed by Eypasch in the 1990s showed poorer QOL outcomes in those with objectively-confirmed oesophagitis compared to those without, at five years follow-up post laparoscopic Nissen fundoplication. [128] The GSRS (Gastrointestinal Symptom Rating Scale) tool is an established tool to provide specific gastrointestinal symptom scores and has been in use for decades. The GSRS is composed of five scales of reflux, abdominal pain, diarrhoea, constipation and indigestion. Revicki et al confirmed the validity of the GSRS in the setting of GORD with an

American population in the 1990s. [118] However, the GSRS remains a symptom-based assessment tool and has not been validated as a quality of life instrument per se.

A multitude of generic quality of life assessment tools have been reported in the literature. A common theme amongst this group is the ability to readily compare general quality of life data from one cohort (such as a study population) against the wider population, provided this is known. A widely-used generic quality of life instrument is the Medical Outcomes/RAND short-form 36 (SF-36) instrument. This tool, developed by Ware and colleagues in the early 1990s, is now available in over fifty languages. The questionnaire consists of thirty-six questions across the eight domains of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. Interpretation of scores is a more exhaustive process that involves transformation of each response into a score between 0-100 which is then standardised against a reference population. Further development of the test has seen the domains contribute disparately to a physical component score (PCS) and mental component score (MCS). A large study involving 533 adult patients with moderate to severe GORD reported the predominant impact upon the pain, social function and mental health subscales within the questionnaire. [133] Gee and colleagues demonstrated improvement in the domains of physical, bodily pain and vitality following laparoscopic Nissen fundoplication in a GORD population. [92]However, the significance of responses to the SF-36 questionnaire in GORD patient groups has been shown to correlate poorly to GORD symptoms. [134] This has in-part driven a demand for quality of life questionnaires to better reflect the impact of reflux related symptoms.

Disease-specific quality of life measures for gastrointestinal reflux disease are likely to be more instructive in mapping clinical outcomes following an intervention such as surgery or medical therapy. These include the Gastro-oesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL), QOLRAD (Quality of Life in Reflux Disease and Dyspepsia) and the GERD-TEST (Gastro-oesophageal Reflux and Dyspepsia Therapeutic Efficacy and Satisfaction Test) instruments. Velanovich and colleagues developed the GERD-HRQL in North America in the

1990s. [126]This ten-item assessment addresses the typical symptoms of GORD by two specific questions relating to heartburn and regurgitation, individually, and a single domain for dysphagia. It also gives an individual domain to overall satisfaction. The GERD-HRQL has been applied to a number of clinical settings including follow up after medical and surgical treatment of reflux disease and as an adjunct during investigations such as gastroscopy. Its creators cite its specificity and simplicity of use as being key attributes to its wide adoption. The QOLRAD is another disease-specific questionnaire which was developed in Europe at a similar time as the GERD-HRQL. [124] It consists of a 25-question inventory incorporating the effect of dyspepsia on the five domains of emotional stress, sleep disturbance, physical and social functioning, eating and drinking, and vitality. The QOLRAD may be seen as somewhat of a hybrid between the reflux-specific and generic quality of life tests as each domain relates to the impact of dyspepsia on one aspect of quality of life without providing additional information on specific GORD symptomatology. The GERD-TEST questionnaire is the most recently developed instrument was published by Nakada and colleagues. [135] The initial study involved outcomes following the medical treatment of GORD in a Japanese cohort with the early, generic Medical Outcome Study Short-Form 8 (SF-8) quality of life questionnaire as a reference. The instrument contains a 13 –item question battery relating to GORD and includes a satisfaction measure. However, the use of the test is in its infancy and its uptake appears limited outside its developers' institution.

The ideal prerequisites for an effective quality of life instrument as proposed by Chassany are a high validity with reliability and responsiveness. One may also add that accessibility be another key consideration as cost-barriers should not interfere with access to useful quality of life instruments. The method of validation remains a vexing issue as a reference standard for comparison between quality of life instruments has not been established. In the absence of a validated reference standard, many authors rely upon older generic instruments such as the Medical Outcome Study short-form 8 (SF-8) and the RAND short-form 36 (SF-36) as surrogate quality of life indicators. Clearly no one quality of life instrument completely fulfils the above prescription by Chassany. However, as a reflux-specific quality of life tool, the GERD-HRQL offers disease-specific symptom information within a quality of life context. It has also been widely utilised as an outcome measure

following surgery for GORD which permits current data to be readily compared to that from earlier studies. The Medical Outcomes/RAND short-form 36 (SF-36) remains the most widely used generic quality of life instrument. It is readily accessible for study use and local data exists for standardisation and interpretation of results for each subscale within the questionnaire. This allows for comparison of a study cohort against a wider population.

In this study both a disease-specific (GERD-HRQL) and generic quality of life instrument (SF-36, version 1) were used to assess quality of life outcomes. The results were compared to symptom-based clinical outcomes and overall satisfaction ratings obtained from a second questionnaire.

5.2 Methods

A full description of study methods is detailed in Chapter 2. The study population was recruited following analysis of a prospective surgical unit database which collected demographic, operative and follow-up data for patients undergoing laparoscopic Nissen fundoplication for objectively confirmed GORD between 1991 and 1996. No baseline quality of life measures were available for study participants. Invitation to participate in the study was via mail-out of study letters to patients together with surveys on clinical and quality of life outcome measures. The clinical outcomes of this cohort are recorded in Chapters 3 and 4. Patients who did not have minimum demographic or operative details recorded in the surgical database were not included in the study. An invitation to participate in the study was not mailed to individuals who had previously declined further surgical follow-up or participation in future clinical studies.

5.2.1 Clinical Outcomes

Clinical outcome data is reported in Chapters 3 and 4. In brief, visual-analogue scores (range 0-10) were recorded for each patient to document the severity of the heartburn, regurgitation and dysphagia to liquids and solids. A higher score corresponded to a more significant symptom severity. A global satisfaction score was also recorded using the same scale where a higher score corresponded to higher satisfaction following surgery.

5.2.2 GORD-HRQL

Total score was calculated by summing individual scores from questions 1 through to 15 of the questionnaire (range 0-75). A score of 75 reflects an individual with the worst symptoms possible as per self-reported response, whereas a score of 0 indicates a patient who is symptom-free from GORD.

Total heartburn score was calculated by summing individual scores from questions 1 through to 6 (range 0-30). Similarly, a total regurgitation score was calculated by summing scores from

questions 10 through to 15 (range 0-30). A score of 30 reflects an individual who is experiencing the worst heartburn or regurgitation symptoms possible per self-report, whereas a score of 0 indicates a patient who does not have any heartburn or regurgitation symptoms. Following an analysis by Hunter et al (1996) a total heartburn or regurgitation score less than or equal to twelve with no individual question response greater than two is considered symptom elimination.

5.2.3 Short-Form 36 (SF-36) version 1.0

Responses for each 36 item were collated for each individual who returned the questionnaire. Conversion of each score within a range 0-100 was completed using template readily available from RAND website. For each response a higher number corresponds to a higher level of quality of life. Each subscale score was then normalised to a z score. A mean average of each subscale was then calculated. Using published local population age-standardised normal values, the physical component score and mental component scores were then calculated using methods previously published by Ware et al.[136] A score of 50 in either the mental or physical component score corresponded to the population average within the reference age range. A score below 50 indicated poorer quality of life outcomes and a score above 50 indicated better quality of life outcomes compared to the reference population.

A final subscale relates to reported health transition, which relates to perception of health compared to one year prior. This subscale does not contribute to the physical or mental health component scores.

Table 5-1 Short-Form 36 Subscale Description

SF-36 Subscale	Summary
Physical Functioning (PF)	*Impact of health on physical activity*

Social Functioning (SF)	*Impact of health on social activities*
Role – Emotional Functioning (RE)	*Emotional impacts upon usual role*
Bodily Pain (BP)	*Pain impact upon life*
Mental Health (MH)	*Psychological status*
Role – Physical Functioning (RP)	*Physical impacts upon usual role*
Vitality (V)	*Degree of energy*
General Health (GH)	*General health perception*

5.2.4 Data Handling & Statistical Methods

Data was stored in a secured computer database (FileMaker Pro version 13; FileMaker Inc, http://www.filemaker.com). Statistical analysis was undertaken using SPSS version 23 (www.ibm.com/software/products/en/spss-statistics). Spearman rank coefficient was calculated using bivariate analysis of ordinal clinical and quality of life values with the assumption of a monotonic relationship between the two variables. This was reported as a Spearman rho correlation coefficient (r_s). A weak correlation was deemed to be a $r_s = 0.4 - 0.6$. A strong correlation was deemed to be a $r_s > 0.6$. A statistically-significant result was deemed by a P value equal to or less than 0.01, using two-sided analysis.

5.2.5 Ethics

All research was conducted in accordance with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research guidelines (update May

2015).

The study protocol and accompanying material was approved for use by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) who deemed it met the requirements of the National Statement on Ethical Conduct in Human Research, application number 110.16, dated April 27, 2016.

5.3 Results

5.3.1 Survey Response

Two-hundred and fifty-two patients were mailed surveys during the mail-out period. A completed survey to both SF-36 and GORD-HRQL study instruments was received in one hundred and thirteen (45%) individuals. A higher number of completed SF-36 questionnaires were returned (130, 52%) compared to completed GORD-HRQL (125, 50%) questionnaires. Thirteen patients (5.1%) refused study participation as recorded by response to the initial or subsequent study mail-out. Fifteen patients (5.9%) were unable to be contacted due to a change in address. A single patient (0.4%) within this group was notified to the research team as being recently deceased.

5.3.2 Survey Respondents – Cohort Data

5.3.2.1 Demographics

GERD-HRQL completed questionnaires were returned for 125 individuals (88 male, 37 female). Participants responding to the GERD-HRQL survey were mean age of 67.4 years (SD 10.8), median 68 years (IQR 14). Baseline body-mass index was available for a majority of the respondents. Mean cohort BMI was 27.2 kg/m2 (SD 4.3). Reoperations were recorded in 15 patients (12%). For GERD-HRQL respondents the mean follow up was 264 months (SD 16.1) and median 263 months (IQR 28).

Completed SF-36 quality of life outcome surveys were returned in a total of 130 patients, 91 male (70%) and 39 female (30%). Mean age at follow-up was 67.1 years (SD 10.7). Mean cohort BMI was 27.0 kg/m^2 (SD 4.3). Reoperation after twenty years of follow-up was required in eighteen individuals (14%). Mean interval of follow-up was 264 months (SD 16); median 263 months (IQR 27.2).

Table 5-2 Baseline Demographic and Operative Data – Respondents to QOL Questionnaire

	GERD-HRQL Respondents	SF-36 Respondents
Age (mean)	67.4 (SD 10.8)	67 (SD 11)
Gender M:F	70:30	70:30
BMI (kg/m2)	27.2 (SD 4.3)	27.0 (SD 4.3)
Reoperation	12%	14%

5.3.3 GERD-HRQL

One-hundred and twenty-five respondents completed the GERD-HRQL questionnaire representing a mean follow period of 263 months (SD 16.1) and median 263 months (IQR 28).

The mean total score for those returning surveys was 6.2 (SD 11.1).

Mean heartburn score = 3.0 (SD 5.2)

Mean regurgitation score = 2.0 (SD 4.8)

Table 5-3 Response to GERD-HRQL global satisfaction question (Q11)

	SATISFIED	DISSATISFIED	NEUTRAL
N	102	10	13
%	81.6	8	10.4

Mean heartburn score 3.0 (SD 5.2)

Mean regurgitation score 2.0 (SD 4.8)

A total of one-hundred and two respondents (81.6%) reported satisfaction from treatment. Ten patients were dissatisfied (8%) and thirteen remained neutrally satisfied (10.4%).

5.3.4 GERD-HRQL - Correlation to Symptom Scores

A significant correlation was identified between post-operative heartburn severity (VA 0-10) and total GORD-HRQL score (P = 0.001).

Table 5-4 Correlation of symptoms by Clinical and GERD-HRQL Questionnaire

Clinical Variable	HRQL Variable	r_s	P
Heartburn (VA 0-10)	HRQL Q1 Heartburn	**0.76**	< 0.001
Heartburn (VA 0-10)	HRQL Heartburn Composite Sum	**0.75**	< 0.001
Regurgitation (VA 0-10)	HRQL Q10 Regurgitation	**0.76**	< 0.001
Regurgitation (VA 0-10)	HRQL Regurgitation Composite Sum	**0.79**	< 0.001
Dysphagia Liquids (VA 0-10)	HRQL Q7 (Dysphagia)	**0.54**	< 0.001
Dysphagia Solids (VA 0-10)	HRQL Q7 (Dysphagia)	**0.76**	< 0.001
Global Satisfaction	HRQL (TOTAL)	**-0.49**	< 0.001

Score (VA 0-10)			
Nb. Correlation considered significant if r_s > 0.4 or < -0.4 and P <0.01			

5.3.5 Short-Form 36 (SF-36)

Completed SF-36 quality of life outcome surveys were recorded in a total of 91 male (70%) and 39 female (30%). Mean interval of follow-up was 264 months (SD 16); median 263 months (IQR 27.2). Average responses to SF-36 subscales are reported in Table 5.4. Comparison was made to local population data using the Health Omnibus Study.[137] Given a mean age of 67 in SF-36 respondents, mean values for each subscale were less than the 65-74 age group population comparator.

Table 5-5 Mean values for SF-36 Subscales for Study Cohort and local population data*

	Fundoplication Cohort	AGE 65-74	AGE 75+
Physical Functioning	**66.5** (SD 29.2)	72.7	56.4
Role limitation Physical	**62.3** (SD 44.6)	66.4	55.4
Role limitation Emotional	**75.6** (SD 38.4)	87.7	85.7
Energy/Vitality	**54.0** (SD 22.4)	61.9	56.2
Emotional Well	**75.7**	81.9	81.3

being	(SD 19.5)		
Social Functioning	**75.7** (SD 27.0)	85.1	81.0
Pain	**66.4** (SD 28.4)	70.8	66.9
General Health	**62.1** (SD 22.6)	65.8	62.5

*Compared to South Australian Population norms from 2002 (Health Omnibus Study)

Composite data for physical and mental component scores standardised to local population data were:

Physical Component Score (PCS) = 49.3 (SD 10.9) **(Population Normal Value = 50)**
Mental Component Score (MCS) = 44.4 (SD 12.7) **(Population Normal Value = 50)**

Reported health transition = not recorded

5.3.6 Short-Form 36 (SF-36) – Correlation to Clinical Symptom Scores

Visual-analogue clinical ratings for heartburn and satisfaction with surgery were checked for correlation with SF-36 subscales and aggregated physical/mental composite scores. No significant correlation was found between any SF-36 subscale/composite score and heartburn or satisfaction ratings (Table 5.6)

Table 5-6 Correlation (r_s) of heartburn and satisfaction scores with SF-36 responses

SF-36 Domain	Heartburn Visual Analogue Score (0-10)	P
Physical Functioning	-0.173	0.049
Social Functioning	-0.187	0.033
Role Limitation (Emotional)	-0.271	0.002
Bodily Pain	-0.209	0.017
Mental Health/Emotional Well Being	-0.193	0.028
Role Limitation (Physical)	-0.158	0.073
Energy/Vitality	-0.183	0.037
General Health	-0.139	0.116
Nb. Correlation considered significant if r_s > 0.4 or < -0.4 and P <0.01		

SF-36 Domain	Satisfaction Visual **Analogue** Score (0-10)	P
Physical Functioning	0.126	0.152
Social Functioning	0.229	0.009
Role Limitation (Emotional)	0.121	0.170
Bodily Pain	0.235	0.007
Mental Health/Emotional Well Being	0.262	0.003

Role Limitation (Physical)	0.104	0.238
Energy/Vitality	0.182	0.038
General Health	0.255	0.003
Nb. Correlation considered significant if r_s > 0.4 or < -0.4 and P <0.01		

	Physical Component Score		**Mental Component Score**	
	r_s	P	r_s	p
HB (VA 0-10)	-0.111	0.210	-0.248	0.004
Satisfaction (VA 0-10)	0.129	0.143	0.269	0.002

5.4 Discussion – Quality of Life Outcomes

Gastro-oesophageal reflux impacts upon patient quality of life but instruments to measure quality of life changes have shown mixed value when applied in the setting following laparoscopic Nissen fundoplication surgery. This analysis used both a generic and disease-specific QOL instrument as a means of mapping patient outcomes which was then compared to clinical symptom scores. This study demonstrated a strong correlation between the GERD-HRQL quality of life measures and patient symptoms at up to 22 years post laparoscopic Nissen fundoplication. Conversely, domains within the SF-36 survey did not correlate with patient symptom scores.

It has been demonstrated that the SF-36 scores in both physical and mental component scores are impacted detrimentally by active gastro-oesophageal reflux disease. [133] Further, multiple studies have shown improvement in SF-36 domains following laparoscopic Nissen fundoplication surgery for GORD.[138-140] A clear limitation in this study is a lack of baseline quality of life data and as such improvements in quality of life parameters following surgery cannot be demonstrated. In place of baseline QOL data, the current study utilised comparison with published age-standardised local SF-36 subscales. This generated comparable results for the summarised physical component scale (PCS) but showed a lower than expected mental component scale (MCS). This result is inconsistent with the findings of Koetje et al (2016) who reported near-normal MCS post fundoplication at 24 months while PCS measures remained below the population norm. In the current study, all SF-36 subscales were lower than that population (age-adjusted) normal values. The reason for this is not immediately clear but multiple respondents documented other chronic illnesses that they stated influenced their answers on returned questionnaires. The study instruments were not designed to incorporate answers relating to other chronic diseases so this remains a possible confounding factor in the results.

The mean GERD-HRQL score of 6.2 for the study respondents compares favourably with other studies such as Gee et al (2008) where the mean score was 5.7, albeit using a much shorter follow-up interval. [92] Unfortunately the overall score using the GERD-HRQL has more utility when compared to baseline in the assessment of an intervention such as medical therapy or

surgery. Further, Velanovich cited a further limitation in that the questionnaire has a poor correlation with the atypical symptoms of GORD (such as respiratory symptoms or chest pain).[141]

5.5 Conclusions – Quality of Life Outcomes

The disease-specific GERD-HRQL questionnaire correlates closely to clinical symptom scores in the long-term follow-up of gastro-oesophageal reflux disease following laparoscopic Nissen fundoplication. Further, the instrument could be justifiably recommended as a quasi-standard for reporting quality of life outcomes in antireflux surgery. No significant correlation was found between any SF-36 domain and symptom scores. The current findings suggest the laparoscopic Nissen fundoplication procedure may be associated with lower scores in the Mental Component Score composite of the SF-36 questionnaire, however the clinical utility of this finding remains unknown.

CHAPTER 6 RANDOMISED TRIAL OF DIVISION VERSUS NON DIVISION OF SHORT GASTRIC VESSELS DURING NISSEN FUNDOPLICATION: 20 YEAR OUTCOMES

The information contained in this thesis chapter formed the basis of the publication

Kinsey-Trotman SP, Devitt PG, Bright T, Thompson SK, Jamieson GG, Watson DI. Randomized Trial of Division Versus Nondivision of Short Gastric Vessels During Nissen Fundoplication: 20-Year Outcomes. Annals of surgery. 2018 Aug 1;268(2):228-32.

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CHAPTER 7 DISCUSSION

This descriptive study reported the clinical outcomes reported from 152 patients of mean follow-up of 265 months. This represents the longest period of follow-up for a laparoscopic Nissen fundoplication cohort currently known. Further, the current study represents what is believed to be the largest body of outcome data of a laparoscopic Nissen fundoplication case-series with follow-up exceeding eleven years. Specifically, the study response rate of 60% compares favourably against previous studies of follow-up exceeding ten years. By including those patients who are recorded as deceased or otherwise incapacitated in the analysis, it can be stated that the twenty-year outcomes are known in over half of the patient series (52%) contained in the surgical database. This is a significantly higher than the study by Cowgill et al which reported the eleven year outcomes from 239 patients from a total prospective database of 829 patients (28%). The current study also compares favourably with the two ultra-long term follow-up case series by Luostarinen and Robinson from the open and laparoscopic realm, respectively. The Finnish case-series reported a response rate of 54% which was from a small total cohort of 45 patients. The American case series by Robinson et al reported a response rate of one third from a total cohort number of one-hundred and ninety-three.

The primary aim of the study was to assess control of heartburn and other typical symptoms of GORD at ultra-long term follow-up. The study demonstrated a high rate of heartburn control as evidenced by eighty-four percent of respondents remaining heartburn-free or with infrequent heartburn with low mean visual analogue heartburn scores. Similar results were also found for regurgitation. These results do not differ significantly from the long-term follow-up data from local and overseas studies reporting outcomes between ten and fifteen years post fundoplication (which did not differ significantly from shorter intervals such as five years). No significant differences were found in the report of new complications (such as port site herniae) or requirement for revisional surgery which were both uncommon (< 5%) after ten years follow-up. It could then be argued that the routine follow-up of patients with complicated reflux disease following five years is of limited utility.

A potential confounder to this analysis is the use of proton-pump inhibitor medication which was reported in thirty-nine percent of respondents. The indication and frequency of individual use of antireflux medication by respondents remains unknown. Similar studies have significantly different methods of reporting PPI use which makes direct comparison difficult. Further, the precise indication for this medication group in this setting is frequently for symptoms other than heartburn. The current study mirrors others which show higher PPI use at longer follow-up intervals. In part this is very likely to be influenced by the ready access to this medication group both by prescription subsidy on the local Pharmaceutical Benefits Scheme and via pharmacist supply 'over the counter' for almost a decade in Australia. It is noteworthy that the majority of respondents had undergone their primary antireflux surgery for medication-refractory heartburn with most taking higher regular doses of omeprazole preoperatively. This study found that these patients were at least medication-responsive at twenty-two years follow-up, an effect which cannot be reliably explained by a change to alternative PPI as efficacy does not change significantly across this medication group. Further, a subset of the above patients were taking antireflux medication on an ad-hoc basis based on information contained in returned questionnaires, although this was not formally assessed using the study instrument. It could therefore be surmised that the laparoscopic Nissen fundoplication remains efficacious at long follow-up intervals exceeding twenty years in a large number of individuals.

The lack of objective tests such as endoscopy or pH monitoring may be a criticism of the current study. However, as previously stated, the acceptability of these investigations, particularly in symptom-free individuals remains a barrier to their application. Further, the degree to which these tests can verify both efficacy and tolerability of the Nissen fundoplication technique remains doubtful. As has been demonstrated, patient symptom scores do not always reflect the findings on these tests and there remains considerable barriers in terms of healthcare resource availability to their use in research.

A vexed issue remains how to assess the tolerability of the procedure at long-term follow-up. This is largely due to the nature of gastrointestinal symptoms being non-specific to any particular treatment side-effect or disease process. The incidence of any dysphagia symptom amongst

respondents was reported in just over one half but was not statistically-significantly higher than preoperative. Reassuringly, post-operative mean visual analogue scores for dysphagia were lower than preoperative (non-significant). As with other symptoms, comparison with similar studies is limited by variations in reporting methods. The above study by Robinson et al reported an absolute rate of dysphagia of 47% but those experiencing it as a daily symptom of 16%. The current study showed only three percent of respondents experiencing dysphagia as a daily symptom with no respondents reporting dysphagia with every meal. A unique aspect to the study is the documentation of a large array of non-specific and atypical gastrointestinal symptoms such as flatus, nocturnal cough and epigastric bloat. The most common 'other symptom' reported was increased flatus with just over half of respondents selecting this as a symptom. This symptom did not feature as a significant troublesome symptom. In comparison epigastric bloat was experienced in a similar number of respondents with just under one quarter unable to relieve bloat symptoms. Epigastric bloat was deemed to be the most troublesome symptom for nine percent. The study by Salminen et al of a much smaller cohort combined abdominal bloat and flatulence symptoms and stratified by symptom severity. After fifteen years follow-up, only five percent of patients were free from these symptoms with twenty-three percent reporting severe symptoms. A difficulty when expressing symptoms at extended follow-up intervals remains to what degree one should attribute the current symptoms to the original surgery? The current study did not endeavour to answer this question but included the vast array of possible gastrointestinal symptoms for completeness. Overall, frequent or troublesome symptoms were an uncommon report which suggests the procedure is tolerated by most patients at twenty years follow-up and beyond. This finding was supported by low quality of life index scores in the disease-specific HRQL survey. No strong correlation was found between patient symptom scores and domains within the short-form 36 survey. These findings are similar to those reported previously. A limitation with interpreting the quality of life indices was a lack of baseline comparative data for the cohort. Comparison therefore was limited to previously published values for the HRQL instrument from similar studies and standardisation against values obtained for similar aged persons from local studies using the short-form 36 survey. Notably the survey respondents had a lower result for the aggregated mental component score in the SF36. Prior studies have shown poor reflux control impacting

predominantly upon the domains of pain, social function and mental health. The SF36 findings seem incongruent with the clinical findings which showed a majority of patients achieving good heartburn, hence poor symptom control is unlikely to be a factor in the findings from the SF36 survey.

The study findings do not support the routine division of the short gastric vessels during laparoscopic Nissen fundoplication. While overall outcome in terms of heartburn control and dysphagia rates are similar with- and without division of the short gastric vessels, an association of the former with epigastric bloating symptoms was found at follow-up intervals to twenty years. This is not a new finding as it has been observed at an earlier follow-up interval from the randomised trial from which it is derived, which also formed part of a meta-analysis by Engstrom et al in 2011. [145] In a subsequent meta-analysis by Khatri et al, bloating symptoms were similar between treatment groups. [146] Earlier research from the above Swedish group suggested preservation of the short-gastric vessels was more likely to preserve venting reflexes within the stomach. [147] It is likely that any perceived advantage for routine division of the short-gastric vessels during laparoscopic Nissen fundoplication will continue to be debated. However, the findings from this study reaffirm previous findings that there is no difference in terms of efficacy between the two techniques but tolerability may be reduced when the short-gastric vessels are divided.

CHAPTER 8 CONCLUSION

The laparoscopic Nissen fundoplication technique provides durable efficacy in gastro-oesophageal reflux disease with acceptable tolerability at ultra-long term follow-up intervals of up to 22 years. Routine division of the short-gastric vessels during fundoplication does not impart any clinical benefit but may increase the likelihood of postoperative bloat symptoms. The disease-specific quality of life HRQL instrument correlates highly with patient symptom scores following antireflux surgery.

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APPENDICES

8.1 Appendix I:

LAPAROSCOPIC FUNDOPLICATION

LONG-TERM FOLLOW-UP PROJECT

Your time spent completing this questionnaire is greatly appreciated.

Please place the questionnaire in the reply paid envelope to assist its return to the research team at Flinders Medical Centre.

Name: _____ Date Questionnaire completed: / /

Has your address changed from the one on the front of this envelope? If so, please provide new details:

_____

In case we need to contact you to check any answers, could you provide us with your telephone numbers:

Home: _____ Mobile: _____

Work: _____ email: _____

1) Have you had any of the following tests or procedures since your original surgery? (Please Tick)
☐Endoscopy ☐Oesophageal Manometry (tube in the nose) ☐Barium swallow X-ray

☐Dilatation ☐24 hr pH (small tube in the nose for a day) ☐Other:_____

2) **HEARTBURN** *(burning sensation behind the lower chest)*

a) Please grade the ***severity*** of any heartburn you currently experience by circling a number from 0 to 10

Heartburn *severity* **AFTER** surgery (**NOW)**

0----1----2----3----4----5----6----7----8----9----10

(0=no heartburn) (10=severe heartburn)

b) How often to you experience heartburn? Please tick *one* in the list below:

Heartburn *frequency* **AFTER** surgery (**NOW)**

☐Never ☐Occasionally ☐ Monthly ☐Weekly ☐Daily ☐Each Meal

3) **REGURGITATION** *(food or fluid rising into the mouth)*

a) Please grade the ***severity*** of any regurgitation you experience by circling a number from 0 to 10:

Regurgitation *severity* **AFTER** surgery (**NOW)**

0----1----2----3----4----5----6----7----8----9----10

(0=no regurgitation) (10=severe regurgitation)

b) How often do you feel food or fluid rising *(regurgitation)*? Please tick *one* in the list below.

Regurgitation *frequency* **AFTER** surgery (**NOW)**

☐Never ☐Occasionally ☐ Monthly ☐Weekly ☐Daily ☐Each Meal

4) **DYSPHAGIA** *(food sticking in the gullet/food pipe or difficulty swallowing)*

a) Do you have difficulty swallowing any food or liquids or do they get stuck in your food pipe/gullet?
☐Yes ☐No

b) How often do you have difficulty swallowing *(or food sticking in the food pipe)?* Please tick *one* in the list below:

Difficulty swallowing *frequency* **AFTER** surgery (**NOW)**					
☐Never	☐Occasionally	☐ Monthly	☐Weekly	☐Daily	☐Each Meal

c) Please grade the ***severity*** of any difficulty in swallowing *(or food sticking in the food pipe)*for **LIQUIDS** and **SOLIDS** by circling a number from 0 to 10:

Difficulty in swallowing **LIQUIDS**

severity **AFTER** surgery (**NOW)**

0---1----2----3----4----5----6----7----8----9----10

(0=no difficulty) (10=severe difficulty)

Difficulty in swallowing **SOLIDS**

severity **AFTER** surgery (**NOW)**

0---1----2----3----4----5----6----7----8----9----10

(0=no difficulty) (10=severe difficulty)

5) **<u>OTHER SYMPTOMS</u>**

a) Please tick the boxes below ☑ to indicate any *other* symptoms you have **now**:

AFTER surgery **(NOW)**	Symptoms
☐	Pain around top of stomach region

- ☐ Pain on swallowing
- ☐ Fullness in the stomach after eating or early fullness with eating
- ☐ Unable to belch or burp
- ☐ Bloating of the stomach
- ☐ Inability to relieve bloating *(If you suffer from bloating)*
- ☐ Nausea *(feeling sick)*
- ☐ Vomiting
- ☐ Coughing at night
- ☐ Wheezing at night
- ☐ Choking attacks at night
- ☐ Increased passage of wind from the bowel
- ☐ Diarrhoea *(loose bowel motions)*
- ☐ Chest pain
- ☐ Shortness of breath
- ☐ I don't have any of these symptoms

6) Which **ONE** of these symptoms troubles you ***most CURRENTLY*** (including heartburn, difficulty in swallowing and regurgitation)? _____

7) Are you taking any medications for heartburn? Yes / No

If yes; which ones?

☐Esomprazole (Nexium®) ☐Cimetidine (Magicul®) ☐AluTab®

☐Lansoprazole (Zoton®) ☐Famotidine (Pepzan®) ☐Gaviscon®

☐Omeprazole (Losec®) ☐Nizatidine (Tazac®) ☐Mylanta®

☐Pantoprazole (Somac®) ☐Ranitidine (Zantac®) ☐Tums®/Rennie®/Salvital®

☐Rabeprazole (Pariet®) ☐Other Antacid

☐Sucralfate (Ulcyte®)

If you are taking any other medication for heartburn which is not listed, please tell us what it is;

…….

……..

8) Outcome: Would you consider the outcome of your surgery to **currently** be: (tick one)

☐ Excellent *(complete recovery)*

☐ Good *(major improvement with minor problems)*

☐ Fair *(major improvement with still significant problems or adverse effects)*

☐ Poor *(minor or no improvement or deterioration)*

9) Relating to your original surgery, would you consider yourself to have: (tick one)

☐ 1: No symptoms

☐ 2: Mild symptoms which are easily controlled by simple care such as avoiding certain foods or small meals

☐ 3: Moderate symptoms which are not controlled by simple care, but are not interfering with your social life or work.

☐ 4: Moderate symptoms which are interfering with your social life or work.

☐ 5: Symptoms which are as bad or worse than they were before your original surgery.

10) **SATISFACTION OF SURGERY**

Please indicate how satisfied you are with your surgery by circling a number from 0 to 10:

Satisfaction of Surgery *score*
0---1----2----3----4----5----6----7----8----9----10
(0=unsatisfied) (10=completely satisfied)

11) Having gone through this operation and knowing now what is involved, would you have made the same decision to have the same operation for the same problem (In other words, do you think you made the correct decision when you agreed to have the operation)?

☐Yes ☐No

SF36 Questionnaire

The following questions relate to your views about your health. Please select only one choice for each item

I) In general, would you say your health is:
☐Excellent ☐Very Good ☐Good ☐Fair ☐Poor

II) Compared to **ONE YEAR AGO**, how would you rate your health in general NOW?
☐ **MUCH BETTER** than one year ago
☐ Somewhat **BETTER** now than one year ago
☐ About the **SAME** as one year ago
☐ Somewhat **WORSE** now than one year ago
☐ **MUCH WORSE** now than one year ago

III) Does your health now limit you in these activities? If so how much?

Vigorous activities such as running, heavy lifting or strenuous sports?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, golf?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Lifting or carrying groceries?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Climbing **several flights** of stairs?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Climbing **ONE flight** of stairs?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Bending, kneeling or stooping?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Walking **MORE THAN** 1 kilometre?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Walking **several** hundred metres?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Walking **one** hundred metres?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

Bathing or dressing yourself?
☐Yes, limited a lot ☐Yes, a little limited ☐No, no limited at all

IV) During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities as a result of your physical health?

Cut down on the **amount of time** you spent on work or other activities?
☐Yes ☐No

Accomplished less than you would like?
☐Yes ☐No

Were limited in the **kind** of work or other activities?
☐Yes ☐No

Had **difficulty** performing the work or other activities (for example it took more effort)?
☐Yes ☐No

V) During the **past 4 weeks**, had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down on the **amount of time** you spent on work or other activities?
☐Yes ☐No

Accomplished less than you would like?
☐Yes ☐No

Didn't do work or other activities as **carefully** as usual?
☐Yes ☐No

VI) During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?
☐Not at all ☐Slightly ☐Moderately ☐Quite a bit ☐Extremely

VII) How much **bodily pain** have you had during the **past 4 weeks**?
☐None ☐Very Mild ☐Mild ☐Moderate ☐Severe ☐Very Severe

VIII) During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?
☐Not at all ☐A little bit ☐Moderately ☐Quite a bit ☐Extremely

IX) These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks…**

a) Do you feel full of pep?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

b) Have you been a very nervous person?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

c) Have you felt so down in the dumps that nothing could cheer you up?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

d) Have you felt calm and peaceful?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

e) Did you have a lot of energy?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

f) Have you felt downhearted and blue?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

g) Do you feel worn out?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

h) Have you been a happy person?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

i) Did you feel tired?
☐All of the time ☐Most of the time ☐A good bit of the time
☐Some of the time ☐A little of the time ☐None of the time

X) During the **past 4 weeks**, how much of the time has your **physical health** or **emotional problems** interfered with your social activities (like visiting friends, relatives etc.)?
☐All of the time ☐Most of the time ☐Some of the time ☐A little of the time
☐None of the time

XI) How TRUE or FALSE is **each** of the following statements for you?

a) I seem to get sick a little easier than other people?
☐Definitely True ☐Mostly True ☐Don't know ☐Mostly False ☐Definitely False

b) I am as health as anybody I know?
☐Definitely True ☐Mostly True ☐Don't know ☐Mostly False ☐Definitely False

c) I expect my health to get worse?
☐Definitely True ☐Mostly True ☐Don't know ☐Mostly False ☐Definitely False

d) My health is excellent?
☐Definitely True ☐Mostly True ☐Don't know ☐Mostly False ☐Definitely False

HRQL

The following questions require a symptom score to be given between 0 and 5 where:

0 = no symptom at all

1 = symptom noticeable but not bothersome

2= symptom noticeable and bothersome but not every day

3= symptom bothersome every day

4= symptom affect daily living

5 = symptom is incapacitating to do daily activities

Please check the box to the right of each question which best describes your experience over the past 2 weeks.

1.	How bad is the heartburn?	0☐	1☐	2☐	3☐	4☐	5☐
2.	Heartburn when lying down?	0☐	1☐	2☐	3☐	4☐	5☐
3.	Heartburn when standing up?	0☐	1☐	2☐	3☐	4☐	5☐
4.	Heartburn after meals?	0☐	1☐	2☐	3☐	4☐	5☐
5.	Does heartburn change your diet?	0☐	1☐	2☐	3☐	4☐	5☐
6.	Does heartburn wake you from sleep?	0☐	1☐	2☐	3☐	4☐	5☐
7.	Do you have difficulty swallowing?	0☐	1☐	2☐	3☐	4☐	5☐
8.	Do you have pain with swallowing?	0☐	1☐	2☐	3☐	4☐	5☐
9.	If you take medication, does this affect your daily life?	0☐	1☐	2☐	3☐	4☐	5☐

10.	How bad is the regurgitation?	0☐	1☐	2☐	3☐	4☐	5☐
11.	Regurgitation when lying down?	0☐	1☐	2☐	3☐	4☐	5☐
12.	Regurgitation when standing up?	0☐	1☐	2☐	3☐	4☐	5☐
13.	Regurgitation after meals?	0☐	1☐	2☐	3☐	4☐	5☐
14.	Does regurgitation change your diet?	0☐	1☐	2☐	3☐	4☐	5☐
15.	Does regurgitation wake you from sleep?	0☐	1☐	2☐	3☐	4☐	5☐

16. How satisfied are you with your present condition?

Satisfied☐ Neutral☐ Dissatisfied☐