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CLINICAL AND ONCOPREVENTIVE OUTCOMES OF ANTIREFLUX SURGERY

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Clinical and oncopreventive outcomes of antireflux surgery
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Gastro-oesophageal reflux disease (GORD), with heartburn and acid regurgitation as main symptoms, is a common disease with increasing prevalence. GORD is associated with oesophageal adenocarcinoma, a cancer with demanding treatment and yet poor prognosis. GORD is typically managed with pharmacological treatment, mainly using proton pump inhibitors, or through laparoscopic antireflux surgery. The aim of this thesis was to evaluate outcomes of antireflux surgery, i.e. safety, effectiveness and prevention of oesophageal adenocarcinoma.

Study I and II were nationwide Swedish cohort studies based on data from the Patient Registry, Causes of Death Registry, Registry of the Total Population (in study I only), and the Swedish Prescribed Drug Registry (in study II only). **Study I** assessed safety aspects with focus on the risk of mortality, reoperation and prolonged hospital stay among patients of working age who underwent primary laparoscopic antireflux surgery for GORD. In addition, it provided descriptive data regarding trends and comorbidities among patients who had undergone such surgery. The study found low risks of mortality (0.08%) and reoperation (0.4%) within 90 days of surgery. Patients of female sex, and older age and with more comorbidities had an increased risk of prolonged hospital stay. Generally, the number of patients who underwent antireflux surgery in Sweden decreased substantially during the period, while the proportion with severe comorbidities among the operated patients increased over time. **Study II** assessed the risk of recurrence of reflux symptoms following primary laparoscopic antireflux surgery for GORD, using reoperation or prescribed medications against reflux (exceeding six months of treatment) as the measures of this outcome. The reflux recurrence rate was 17.7% during the median follow-up of 5.6 years, and the majority of patients (83.6%) had medical treatment. Female sex, older age, and comorbidity were associated with an increased reflux recurrence, but hospital volume was not.

Study III was a systematic review and meta-analysis assessing if oesophageal adenocarcinoma can be prevented by antireflux surgery. No clear differences in risk were found when comparing surgery with medication, and the risk of oesophageal adenocarcinoma remained elevated following antireflux surgery compared to the

general background population. **Study IV** was a Nordic cohort study, based on nationwide registries from Denmark, Finland, Iceland, Norway, and Sweden, including patients with GORD. The risk of oesophageal adenocarcinoma was initially high, but decreased over time both following antireflux surgery and presumed medical therapy to a risk in line with that of the general background population after 15 years. The risk of oesophageal adenocarcinoma was similar when directly comparing medical and surgical therapy.

In conclusion, laparoscopic antireflux surgery can be considered a safe and effective treatment option of GORD which is potentially underused in clinical practice, especially among young and otherwise healthy individuals who might otherwise need lifelong medical treatment. Effective treatment of GORD seems to reduce the risk of oesophageal adenocarcinoma.

LIST OF SCIENTIFIC PAPERS

I. Maret-Ouda J, Yanes M, Konings P, Brusselaers N, Lagergren J.
Mortality from laparoscopic antireflux surgery in a nationwide cohort of the working-age population.
British Journal of Surgery. 2016 Jun;103(7):863-70.

II. Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J.
Association between laparoscopic antireflux surgery and recurrence of gastroesophageal reflux.
JAMA. 2017 Sep 12;318(10):939-946.

III. Maret-Ouda J, Konings P, Lagergren J, Brusselaers N.
Antireflux surgery and risk of esophageal adenocarcinoma: A systematic review and meta-analysis.
Annals of Surgery. 2016 Feb;263(2):251-7.

IV. Maret-Ouda J, Wahlin K, Artama M, Brusselaers N, Färkkilä M, Lynge E, Mattsson F, Pukkala E, Romundstad P, Tryggvadottir L, von Euler-Chelpin M, Lagergren J.
The risk of esophageal adenocarcinoma following antireflux surgery in the five Nordic countries.
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1 INTRODUCTION

Long-standing gastro-oesophageal reflux disease (GORD), with the main symptoms heartburn and acid regurgitation, affects approximately 10 to 20% of the adult population and has become increasingly common during the last decades.[1,2] Besides the symptoms of GORD which can reduce quality of life substantially, GORD also drastically increases the relative risk of developing oesophageal adenocarcinoma, a cancer characterised by increasing incidence, demanding treatment and poor prognosis.

Patient with GORD are primarily treated with medical therapy. An alternative treatment option is surgery, specifically laparoscopic antireflux surgery, which is what this thesis focuses on.

Included in the thesis are three original studies based on data from nationwide registries as well as one systematic review and meta-analysis. The first two studies examine different outcomes of laparoscopic antireflux surgery, including efficiency and safety. The latter two studies, the meta-analysis and one original study, aim to clarify whether antireflux surgery prevents oesophageal adenocarcinoma.

2 BACKGROUND

2.1 THE OESOPHAGUS: ANATOMY AND HISTOLOGY

The oesophagus is a muscular tube connecting the pharynx to the stomach, its length is approximately 25 cm and the average width is 2 cm.[3] The oesophagus functions as a conduit that transports solids and liquids from the mouth to the stomach through peristalsis, but it also enables regurgitation of stomach contents and air through the mouth.[3] The gross anatomy of the oesophagus in relation to the stomach and the directly adjacent abdominal organs is shown in Figure 1. The oesophagus follows the curvature of the vertebral column, and passes through the hiatus of the diaphragm at approximately the height of the 10th thoracic vertebrae, and then deviates to the left and enters the stomach slightly to the left of the midline at the height of the 11th thoracic vertebrae.[3]

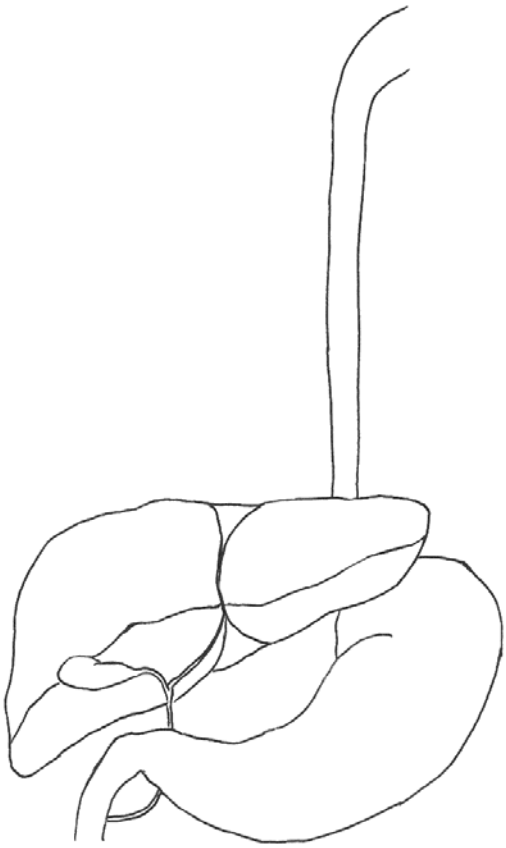


Figure 1. Anatomy of the oesophagus passing behind the left lobe of the liver and entering the stomach. The drawing was made by the author.

The oesophagus receives its arterial blood supply through branches from the inferior thyroid artery (cervical portion), oesophageal and bronchial branches of the thoracic part of the aorta (thoracic portion), and ascending oesophageal branches of the left phrenic and left gastric artery (abdominal portion).[4] The venous blood is drained through the inferior thyroid vein (cervical portion), azygos, hemiazygos, intercostal and bronchial veins (thoracic portion), and the left gastric vein (abdominal portion).[4] Histologically, the oesophagus consists of four main layers; the mucosa, submucosa, muscularis propria and adventitia. The mucosa can be subdivided into three distinct layers; the epithelium, which normally is native non-keratinized stratified squamous epithelium, the lamina propria, consisting of connective tissue, and the muscularis mucosae, which consists of longitudinally arranged smooth muscle bundles.[5] The gastro-oesophageal junction is defined by the start of the longitudinal folds of the proximal stomach. Histologically the junction is defined by where the mucosa changes from oesophageal to gastric epithelium, known as the Z-line, unless there is columnar metaplasia, i.e. Barrett´s oesophagus, which distorts the Z-line.[3] The submucosa consists of loose connective tissue, mainly containing arteries, veins, lymphatic vessels and nodes and nerves.[5] The next layer is, as previously mentioned, the muscularis propria, consisting of two muscle layers: the inner circular and the outer longitudinal layer, and finally the adventitia is mainly constituted by connective tissue.[5] In contrast to the major part of the gastrointestinal system, the oesophagus has no serosa.[5]

2.2 GASTRO-OESOPHAGEAL REFLUX DISEASE

GORD is defined as a "condition that develops when the reflux of duodeno-gastric contents causes troublesome symptoms and/or complications", according to the Montreal definition.[6] GORD occurs when reflux reaches the oesophagus and causes reduced quality of life, reflux oesophagitis or long-term complications, i.e. dysphagia, strictures, Barrett's oesophagus and oesophageal adenocarcinoma.[6,7] The most common symptoms of GORD are heartburn and regurgitation of stomach contents into the oropharynx, and less common symptoms include chest pain, nausea, dysphagia, cough and hoarseness.[8] The majority of patients will remain with a similar grade of severity of GORD over time.[9,10] The prevalence of weekly or severe GORD

is assessed to be 10 to 20% in the western world, however, the prevalence has almost doubled since the mid-1990s.[2] GORD is primarily considered a clinical diagnosis, mainly relying on the clinical presentation and symptoms, and empirical treatment with a proton pump inhibitor (PPI) without endoscopic evaluation can help confirm the diagnosis.[11,12] A mechanism for developing GORD is the development of a hiatus hernia, in which a part of the stomach protrudes or migrates through the diaphragm into the thoracic cavity, thereby, decreasing the integrity of the lower oesophageal sphincter.[13] Hiatal hernias have been reported to be found in approximately 80-90% of GORD patients.[14] There are several environmental risk factors for GORD, and the two most well established are obesity and tobacco smoking. Obesity, and more specifically abdominal obesity, has been determined to increase the risk of GORD symptoms, but also complications of GORD such as oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma.[15,16] Weight loss can increase the chances of reduction of GORD symptoms.[17] Tobacco smoking has been found to be weakly associated with symptoms of GORD, and smoking is also associated with an increased risk of Barrett's oesophagus and oesophageal adenocarcinoma.[15,18-21] Some studies have found an association between consumption of alcohol and GORD symptoms, although causality between alcohol and new onset of GORD have not been found in recent reviews.[15,22-24]

2.3 TREATMENT OF GASTRO-OESOPHAGEAL REFLUX DISEASE

2.3.1 Pharmacological treatment

2.3.1.1 Proton pump inhibitors

The most commonly prescribed, and most effective, pharmacological treatment of GORD is medication using PPI, which irreversibly inhibit H^+/K^+ ATPase in the parietal cells in the gastric epithelium, thus preventing transportation of H^+ across the cell wall suppressing the production of acid in the stomach.[25] Thereby, PPI does not reduce the presence of reflux in itself, but rather reduces the acidity of the refluxate, alleviating symptoms.[26] Treatment with PPI diminishes heartburn in 37 to 61% of patients without oesophagitis, but among patients with oesophagitis, PPI leads to healing of oesophagitis in 72 to 83%, and relief of heartburn in 56 to 77% of the

patients.[27-31] Initial treatment with PPI is once daily, and if sufficient relief of GORD is not achieved, the dose can be increased to twice daily.[32] PPI use has been shown to be superior to treatment with the second most common pharmacological treatment, histamine$_2$ receptor antagonists, both regarding healing of oesophagitis and relieving symptoms of GORD.[29,30] Current clinical guidelines recommend treatment with PPI in the lowest tolerable daily dose as the main treatment for GORD.[33] Attempts should be made to reduce and stop the treatment, however, patients who do not tolerate this might need long-term, sometimes even life-long, treatment.[33] There are some indications from observational studies that long-term treatment with PPI might lead to side-effects, such as an increased risk of hip fractures, *Clostridium difficile*-associated diarrhoea and community-acquired pneumonia, although the evidence is not consistent.[11,34-37] Some studies have also suggested that PPI medication increases the future risk of gastric cancer.[38,39]

2.3.1.2 Histamine$_2$ receptor antagonists

Histamine$_2$ receptor antagonists were introduced in the late 1970's and these are competitive antagonist against histamine receptors in the parietal cells of the stomach, reducing the gastric acidity. Treatment with histamine$_2$ receptor antagonists diminishes heartburn in 48 to 56% of patients, and leads to healing of oesophagitis in approximately 41% of patients.[27,28,30,31,40] Histamine$_2$ receptor antagonists are currently mainly used as a step-down treatment when attempting to stop treatment with PPI.[11] Histamine$_2$ receptor antagonists can also be used to enhance the effectiveness and symptom relief achieved with PPI use.[41]

2.3.2 Antireflux surgery

Antireflux surgery is considered a permanent treatment of severe and well-documented GORD. It is generally considered in three main clinical settings: instead of medication when long-term medication is necessary, against persistent symptoms or damage to the oesophageal mucosa despite high dose medical treatment, or when there is confirmed disruption at the gastro-oesophageal junction, such as large hiatal hernias.[11] The main principle of antireflux surgery (also called fundoplication) is to wrap the fundus of the stomach around the distal oesophagus, a surgical method that

was first described by Rudolph Nissen in 1956, shown in Figure 2.[42] The original antireflux surgery as described by Nissen includes wrapping the fundus completely, 360 degrees, around the distal oesophagus, hence reinforcing the lower oesophageal sphincter. This has been shown to give excellent control of GORD.[43]

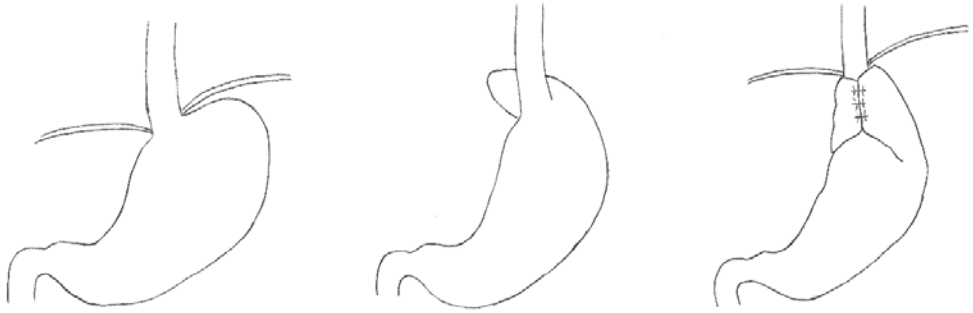


Figure 2. The anatomic alterations achieved through antireflux surgery, in frames 1 and 3 the diaphragm is also seen. Drawing by the author.

However, studies have also shown that there is an increased risk of dysphagia and gas-related symptoms following a complete Nissen fundoplication, and due to this, alternative methods of antireflux surgery have been developed. The most common are the Toupet posterior partial fundoplication, where the fundus is partially wrapped 200-270 degrees posterior of the oesophagus and sutured (first described by André Toupet 1963) and the Dor anterior partial fundoplication, where the fundus is partially wrapped 180 degrees anterior of the oesophagus and sutured (first described by Jacques Dor 1962).[44,45] The introduction of laparoscopic approaches in the 1990's has lowered the operative morbidity rate, the length of the postoperative stay as well as the length of sick leave.[46] Laparoscopic techniques have not been found to improve the results regarding recurrence of gastro-oesophageal reflux, dysphagia, bloating or reoperation, compared to open surgical techniques.[46] Two recent meta-analyses included randomized controlled trials comparing complete laparoscopic antireflux surgery *ad modum* Nissen to either laparoscopic partial antireflux surgery *ad modum* Toupet or laparoscopic partial antireflux surgery *ad modum* Dor.[47,48] The studies showed that reflux control was equivalent following all these procedures, but with significantly lower rate of postoperative dysphagia and lower rate of gas-related symptoms following both Toupet and Dor fundoplications compared to Nissen fundoplication.[47,48] Despite effective initial results, some patients need a redo

antireflux surgery due to recurrence of reflux. A population-based Danish study concluded that 113 of 2,465 patients (4.6%) required a reoperation following primary antireflux surgery, and a large study including 13,050 patients in the United States concluded that 5.2% required reoperation within five years and 6.9% within ten years of the primary surgery.[49,50] A recent Cochrane review including four randomized controlled trials and 1,232 patients concluded that the postoperative results following laparoscopic antireflux surgery were better compared to medical treatment using PPI, both regarding quality of life in the short and long term, but also regarding symptoms of reflux, heartburn and bloating.[43] Earlier studies evaluating antireflux surgery in a long-term setting have determined that a majority of patients (60-90%) were free of symptoms or did not require antisecretory medication at 5-17 years of follow-up.[51-53] Although the risk of complications was low, and mortality rare, these risks are still present in a surgical setting compared to medical therapy.[43] A recent review concluded that based on these results and the risks associated with surgery, medical therapy should be recommended as the first-line treatment for severe GORD.[54] However, among young and healthy individuals with severe symptoms, where very long-term medical treatment otherwise would be needed, surgery should be considered.[54]

2.4 COMPLICATIONS TO GASTRO-OESOPHAGEAL REFLUX DISEASE

2.4.1 Barrett's oesophagus

Following long-term GORD with chronic acid exposure and tissue injury to the epithelium of the oesophagus, the epithelium can heal with a conversion of the cell type, metaplasia, causing squamous cells of the oesophageal lining to be replaced by mucus-secreting columnar cells.[55,56] This epithelium replacing the squamous cells of the oesophagus is referred to as Barrett's oesophagus and is characterised by intestinal-like specialised columnar cells, and although it is generally more resistant to acidic reflux, it is also one of the major and most well established predisposing factors for the development of oesophageal adenocarcinoma.[57] Barrett's oesophagus was first described by the thoracic surgeon Norman Barrett in 1950, and the causality between gastro-oesophageal reflux and Barrett's oesophagus was determined a few years

later.[58,59] The symptoms of Barrett's oesophagus are similar to the symptoms of GORD, hence there are no specific symptoms to distinguish Barrett's oesophagus from GORD, and endoscopy with biopsies with histopathological confirmation is necessary to diagnose Barrett's oesophagus.[32] Recent studies report a specifically increased risk of Barrett's oesophagus among overweight Caucasian men aged over 50 with long term history of GORD.[60] Larger studies that have attempted to estimate the prevalence of Barrett's oesophagus have determined it to be approximately 1.3-1.6% in the adult western population, although some studies have estimated this number to be as high as 5.6%.[61-63] It is still uncertain how high the risk of oesophageal adenocarcinoma is among patients with Barrett's oesophagus, but recent large-scale studies estimate that the rate of progression to oesophageal adenocarcinoma ranges between 0.1 to 0.3% per year in the general population.[64,65] Patients with known Barrett's oesophagus are often monitored with surveillance endoscopy in order to detect dysplasia and early cancers, leading to better survival if cancer occurs.[57,60,66,67] Which patients with Barrett's oesophagus to survey is a matter of debate. A recent consensus statement concluded that patients with Barrett's oesophagus without signs of dysplasia should only be surveyed if they are high-risk patients, i.e. men above 60 years of age with symptoms.[60] Further, patients with low-grade dysplasia should be monitored closely, and if the low-grade dysplasia affects a long segment, is multifocal, and persistent, ablative therapy or endoscopic resection should be performed.[60] High-grade dysplasia should be treated using endoscopic or surgical resection, and in some cases radiofrequency ablation can also be considered.[66]

2.4.2 Oesophageal adenocarcinoma

Oesophageal adenocarcinoma is a malignancy with cellular origin from glandular cells in Barrett's oesophagus. Adenocarcinoma of the oesophagus and gastro-oesophageal junction have been found to be similar regarding pathology and risk factors, and are therefore considered to be the same clinical entity as of the 7th edition of the American Joint Committee on Cancer staging manual.[68,69] The incidence of oesophageal adenocarcinoma has increased drastically during the last four decades, from being a rare histological subtype of oesophageal cancer, to being the most common histological subtype of oesophageal cancer in many western countries.[70,71]

This increase seems to have started in the 1970's and 1980's in many countries, including Sweden, and is continuing still today, as shown in Figure 3.[70,72] There is a strong male predominance of oesophageal adenocarcinoma, which remains unexplained and has remained during the period of increasing incidence. The average male-to-female ratio is approximately 6:1 in western countries, including Sweden.

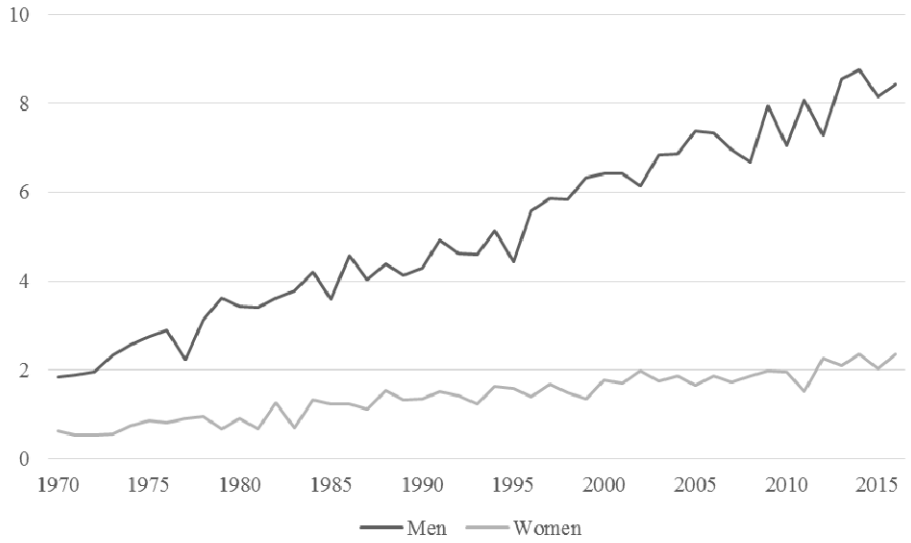


Figure 3. Cases of oesophageal adenocarcinoma per 100,000 adult men and women in Sweden between 1970 and 2016.[73]

2.4.2.1 Symptomatology and diagnosis of oesophageal adenocarcinoma

The most common presenting symptoms of oesophageal adenocarcinoma are progressive dysphagia, developing over a few months, as well as weight loss, fatigue and anaemia.[74] Due to often diffuse or non-present initial symptoms of the tumour, the noticeable symptoms often occur late when the tumour has already started to invade the muscle layers of the oesophagus, and by that time have often metastasised to lymph nodes or distant organs. Therefore, only approximately 25% of the patients present with a localised tumour at the time of diagnosis.[75] Similar to the diagnosis of Barrett's oesophagus, upper endoscopy including biopsies for pathological assessment is the gold standard for diagnosing oesophageal adenocarcinoma. Despite that patients with Barrett's oesophagus are a high risk population, less than 15% of all cases of oesophageal adenocarcinoma are discovered within surveillance programs, mainly because most individuals with Barrett's are never recognised.[76,77]

2.4.2.2 Treatment of oesophageal adenocarcinoma

Due to the fact that oesophageal adenocarcinoma is most commonly discovered at a late stage, one of the most important aspects is to identify patients that might be possible to treat with a curative intent. Following endoscopic evaluation, histological grading, and imaging assessment, an accurate staging can be achieved. For very early and superficial adenocarcinomas (T1a), endoscopic resection or endoscopic ablation is sometimes possible.[74] For locally advanced adenocarcinomas, meaning that the tumour is invading deeper tissues of the oesophagus but without lymphatic spread or distant metastases, surgical treatment is standard therapy. The most common procedure to be performed is oesophagectomy, either with a gastric pull-up, where the mobilised stomach is formed to function as an oesophagus, or with a colonic interposition, where the mobilised colon is replacing the resected oesophagus.[74] The surgical treatment is often accompanied by neoadjuvant chemotherapy or chemoradiotherapy, which has been shown to increase overall survival and rate of radical resection when comparing to surgical therapy alone.[78,79] It remains unclear however, whether neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy is most beneficial regarding long-term survival.[79] Despite recent research regarding treatment of oesophageal adenocarcinoma, the prognosis remains very poor. The overall five-year survival was approximately 5% in 1975, and recent studies have estimated the overall five-year survival to approximately 15-20%.[75,80] Patients with unresectable or metastatic disease are often treated with palliative chemotherapy or chemoradiotherapy.[74] In a palliative setting, endoscopic management and treatment of dysphagia can be important, mainly using stenting of the oesophagus.[74]

2.4.2.3 Risk factors of oesophageal adenocarcinoma

During the late 1990's, it was established that GORD is a main risk factor for oesophageal adenocarcinoma.[81] A meta-analysis including five studies concluded that the odds ratio of developing oesophageal adenocarcinoma was nearly five times higher among individuals suffering from weekly symptoms of gastro-oesophageal reflux (heartburn or regurgitation) compared to those with less frequent or no reflux symptoms (odds ratio 4.92, 95% confidence interval [CI] 3.90-6.22), and increased more than seven times for individuals experiencing reflux symptoms on a daily basis

(odds ratio 7.40, 95% CI 4.94-11.1).[82] Increased body mass index is also associated with an increased risk of oesophageal adenocarcinoma, and a recent meta-analysis of 22 studies concluded that compared to individuals with normal body mass index, the risk ratio was 1.71 (95% CI 1.50-1.96) of developing oesophageal adenocarcinoma if the body mass index is 25-30, and 2.34 (95% CI 1.95-2.81) if ≥30.[83] A pooled analysis of 12 observational studies comparing individuals with body mass index below 25 to those with a body mass index ≥40, the odds ratio of oesophageal adenocarcinoma was 3.65 (95% CI 2.50-5.34).[84] Based on the available literature, a linear association between increased body mass index and risk of oesophageal adenocarcinoma can be seen. A meta-analysis (including 3 cohort and 3 case-control studies) determined that predominantly abdominal or visceral adiposity increased the risk of oesophageal adenocarcinoma significantly, independent of body mass index.[16] Finally, tobacco smoking is associated with a moderately increased risk of developing oesophageal adenocarcinoma. A meta-analysis (including 33 studies) found a risk ratio of 1.76 (95% CI 1.54-2.01), and a pooled analysis (including 10 population-based studies) comparing ever and never smokers found an odds ratio of 2.08 (95% CI 1.83-2.37).[21,85]

2.4.2.4 Prevention of oesophageal adenocarcinoma

A recent meta-analysis, including seven observational studies, concluded that medication with PPI in patients with Barrett's oesophagus decreased the risk of developing oesophageal adenocarcinoma or high-grade dysplasia compared to non-users (odds ratio 0.29, 95% CI 0.12-0.79).[86] This is however debated, and a population-based Danish case-control study found an increased risk of high-grade dysplasia or oesophageal adenocarcinoma despite medication with PPI, both among low- and high-adherence users (relative risk of 2.2, 95% CI 0.7-6.7, and 3.4, 95% CI 1.1-10.5, respectively).[87] However, after adding the Danish study to the meta-analysis previously referred to, an overall protective effect remained.[88] Despite the association between body mass index and oesophageal adenocarcinoma, it is unclear whether weight loss prevents the development of oesophageal adenocarcinoma. This is partially due to unpredictable variations in weight over time and the lack of long-lasting weight loss among obese individuals, hence making it unreliable to use as an

exposure in large cohort studies. Obesity surgery can be regarded a human model to assess if weight loss reduces the risk of oesophageal adenocarcinoma, based on the stable and drastic long-term reduction in weight starting from a specific date.[89,90] A systematic review including 28 studies identified only eleven cases of oesophageal adenocarcinoma following obesity surgery, which made analyses impossible.[91] A recent population-based Swedish cohort study including 34,437 individuals who underwent obesity surgery identified eight cases of oesophageal adenocarcinoma, and no difference in risk of oesophageal adenocarcinoma was seen compared to obese patients that did not undergo obesity surgery.[92] Regarding tobacco smoking, a pooled analysis of ten studies showed that smoking cessation reduced the risk of oesophageal adenocarcinoma over time compared to current smokers.[21] Smoking cessation for less than 10 years was associated with an odds ratio of 0.82 (95% CI 0.60-1.13) and the corresponding number after more than 10 years of cessation was 0.71 (95% CI 0.56-0.89), however, the risk did not decrease to the level of never smokers.[21]

3 AIMS

3.1 OVERALL AIM OF THE THESIS

To estimate outcomes of antireflux surgery regarding safety, effectiveness and prevention of oesophageal adenocarcinoma.

3.2 SPECIFIC AIMS OF THE INCLUDED STUDIES

- To assess the risk of complications and mortality following antireflux surgery.
- To determine the risk of recurrence of gastro-oesophageal reflux following antireflux surgery.
- To estimate the risk of oesophageal adenocarcinoma following antireflux surgery in the published literature.
- To clarify the risk of developing oesophageal adenocarcinoma over time following antireflux surgery in a multinational cohort.

4 MATERIAL AND METHODS

4.1 OVERVIEW

An overview of the methods used in studies I-IV is presented in Table 1.

Table 1. Methods in study I-IV.

	Study I	Study II	Study III	Study IV
Study design	Population-based cohort study	Population-based cohort study	Systematic review and meta-analysis	Population-based cohort study
Data sources	Swedish nationwide registries: Patient Registry, Causes of Death Registry, Registry of the Total Population	Swedish nationwide registries: Patient Registry, Causes of Death Registry, Prescribed Drug Registry	PubMed/MedLine, Web of Science, Cochrane databases	Nordic nationwide registries: Patient Registries, Cancer Registries, Causes of Death Registries and the Swedish Prescribed Drug Registry
Study period	1997-2013	2005-2014	-2014	1964-2014
Inclusion	Patients (age 18-65) undergoing primary laparoscopic antireflux surgery due to gastro-oesophageal reflux disease	Patients (age >18) undergoing primary laparoscopic antireflux surgery due to gastro-oesophageal reflux disease	Patients with gastro-oesophageal reflux disease undergoing antireflux surgery or receiving medication	Patients (age >18) undergoing antireflux surgery due to gastro-oesophageal reflux disease
Outcome	Mortality (within 30 and 90 days), reoperation (within 90 days) and prolonged hospital stay	Recurrence of reflux (prescribed medication >6 months or reoperation)	Oesophageal adenocarcinoma	Oesophageal adenocarcinoma
Cohort members	8,947	2,655	-	942,906
Main statistical analysis	Multivariable logistic regression	Multivariable Cox regression	Fixed-effects Poisson meta-analysis	Standardized incidence ratio and multivariable Cox regression
Co-variables	Age, sex, year of surgery, co-morbidities (Charlson co-morbidity score)	Age, sex, year of surgery, co-morbidities (Charlson co-morbidity score), hospital volume		Standardized incidence ratio: Age, sex, calendar-period Multivariable Cox regression: Age, sex, calendar period, chronic obstructive pulmonary disease, and obesity or diabetes

4.2 DATA SOURCES

4.2.1 The Nordic Patient Registries

All patient registries in the Nordic countries include discharge diagnoses from the in-patient care, and in many cases specialised out-patient care, in each country, and thereby provide longitudinal registration of diagnoses. The diagnoses are registered using the International Classification of Diseases, as well as codes for surgical procedures. Since the late 1990s, the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures is used for coding of surgeries and interventions, which makes it possible to distinguish open and laparoscopic procedures.[93] The year of initiation of the patient registries varies in the different countries. However, due to the mainly publicly funded healthcare in the Nordic countries, the completeness of the registries is high.[94,95] The Danish Patient Registry was founded in 1977 by the Danish Health and Medicines Authority, and nationwide coverage was reached in 1978.[96] Since the initiation, somatic inpatient care was included, and later psychiatric and somatic in- and outpatient care was added.[96] A recent systematic review including 114 studies concluded that the positive predictive value as a measurement of the validity ranged widely (between 15-100%).[97] The Finnish Patient Registry was founded in 1967 by the National Institute for Health and Welfare with nationwide coverage since its initiation. In 1969 the personal identification number was added, enabling linkage to other registries.[98] The registry was renamed to the Finnish Care Register for Health Care in 1994, after which it also included specialised outpatient care and day surgery, and not only somatic inpatient care.[98,99] The Icelandic Patient Registry was founded in 1999 and is managed by the Icelandic Directorate of Health, and data is continuously collected from the hospitals.[100] The Norwegian Patient Registry was founded in 1997, and is managed by the Norwegian Directorate of Health.[101] Both the Icelandic and Norwegian Patient registries have been nationwide since their initiation. The Swedish Patient Registry was founded in 1964, and reached nationwide completeness regarding inpatient healthcare in 1987, and the validity has been determined to range between 85-95% for most diagnoses.[102]

4.2.2 The Nordic Cancer Registries

The Cancer Registries in the Nordic Countries include the date and anatomical and histological codes of all tumours in each country since the year of initiation. Other variables included in the registries vary slightly between the different countries, but generally there are variables corresponding to the geographical localization of the hospital, how the diagnosis was made, whether the tumour was benign or malignant, and if the patient had had a previous tumour. The percentage of cases that are microscopically verified varies between countries, ranging from 93 to 98%.[103] The Danish Cancer Registry was founded in 1942, and registration has been mandatory since 1987.[104] The Finnish Cancer Registry was founded in 1953, with mandatory registration since 1961.[105] The Icelandic Cancer Registry was founded in 1954, and registration has been mandatory since its initiation.[106] The Norwegian Cancer Registry was founded in 1951, and registration has been mandatory since its initiation.[107] The Swedish Cancer Registry was founded in 1958, and registration has been mandatory since its initiation.[108]

4.2.3 The Nordic Causes of Death Registries

The Causes of Death Registries in the Nordic countries share a similar structure. The main variables used in this thesis are date of death, main cause of death and underlying causes of death. These registries in all the Nordic countries have been nationwide and had mandatory registration since their initiation. The years of initiation were 1970 (Denmark), 1969 (Finland), 1952 (Iceland), 1951 (Norway), and 1952 (Sweden).[95] The Swedish Causes of Death Registry has been validated, and the completeness has been determined to be high regarding date of death (100%) and underlying cause of death (96%), and the agreement between death certificates and manually assessed causes of death has been compared and determined to be high.[109-111]

4.2.4 The Swedish Prescribed Drug Registry

The Swedish Prescribed Drug Registry was founded in 1st of July 2005 and contains data on all prescribed and dispensed medications in Sweden from this date. According

to Swedish law, all prescriptions in Sweden have to be reported, and are filed electronically into the registry, which contributes to its nearly 100% coverage.[112]

4.2.5 The Swedish Registry of the Total Population

The population statistics in Sweden was initiated in 1749 and was centralised under the Swedish tax agency in 1962, but managed by Statistics Sweden.[113] The registry contains for example data regarding birth, death, emigration, immigration, marriage, country of birth, sex, and citizenship. It is estimated that the reporting within 30 days is 100% regarding birth and death, 95% regarding immigration, and 91% regarding emigration, and an even higher reporting rate over time.[114]

4.3 SUBJECTS AND METHODS

4.3.1 Study I

4.3.1.1 Design

Nationwide Swedish population-based cohort study.

4.3.1.2 The cohort and the follow-up

The cohort included all patients in Sweden with a diagnosis of GORD who underwent primary laparoscopic antireflux surgery, identified in the Swedish Patient Registry from the NOMESCO code JBC01 (Laparoscopic surgery against gastro-oesophageal reflux). The cohort was restricted to patients of working age, defined as age 18-65 years. Because the study only included patients who had undergone antireflux surgery using a laparoscopic approach, the study period was restricted to range from 1997 onwards, which was the year that the NOMESCO was introduced and separate codes for open and laparoscopic approaches became available. The entire Patient Registry since its initiation was searched for diagnoses representing GORD. The diagnoses used to identify these patients were GORD, heartburn, hiatal hernia, oesophagitis and Barrett's oesophagus. The primary outcome of the study was all-cause and surgery-related 30- and 90-day mortality. Secondary outcomes were reoperation within 90 days and prolonged length of postoperative hospital stay (four days or more). Reoperations were identified with any NOMESCO code beginning with JW

(Reoperation in the gastrointestinal tract). The Swedish Causes of Death Registry was used to identify deaths and underlying causes, and the Swedish Registry of the Total Population was used to calculate the rate of surgery in the entire country. Based on the data in the Patient Registry, the Charlson Co-morbidity Index score was calculated for all patients included in the cohort.[115-119]

4.3.1.3 Statistical methods

All patients who died or underwent reoperation within the cohort were identified and descriptive data of the absolute risk of death within 30 and 90 days following antireflux surgery were retrieved. Due to the low number of deaths, no further analyses could be conducted on this group. Patients undergoing reoperation or requiring prolonged postoperative hospital stay were further analysed using a multivariable logistic regression model determining the odds ratios and 95% CI of reoperation within 90 days of surgery as well as prolonged hospital stay. The regression models were adjusted for age, sex, year of surgery (1997-2002, 2003-2008 or 2009-2013) and co-morbidities (Charlson score 0, 1 or ≥2). Additionally, a spline was fitted modelling the changes in odds ratio for prolonged hospital stay during the study period (as a continuous variable).

4.3.2 Study II

4.3.2.1 Design

Nationwide Swedish population-based cohort study.

4.3.2.2 The cohort and the follow-up

This cohort was collected in a similar way as the cohort in Study I. Based on the Swedish Patient Registry, all patients with GORD (or an associated disorder) who subsequently underwent primary laparoscopic antireflux surgery were identified. The codes used to identify patients with GORD were the same as those in Study I. The patients were linked to the Swedish Prescribed Drug Registry, and due to the year of initiation of the Prescribed Drug Registry, the cohort was restricted to include patients who underwent primary laparoscopic antireflux surgery between 2005 and 2014. To ensure that only primary surgeries were included, all patients who underwent

antireflux surgery (open or laparoscopic) before 2005 were excluded by using the surgical code 4272 before the year 1997, and the codes JBC00, JBC01, JBW96, and JBW97 between 1997 and 2005. The Patient Registry was used to calculate the Charlson Co-morbidity Index score for each included patient at the date of surgery.[115-119] The main aim of the study was to determine the risk of recurrence of reflux symptoms following antireflux surgery. Two different outcomes were defined as a measurement for this: prescribed medication against reflux (PPI or histamine$_2$ receptor antagonists) or secondary antireflux surgery (open or laparoscopic). Medical treatment was identified using the Anatomical Therapeutical Chemical codes A02BC (PPI) and A02BA (histamine$_2$ receptor antagonists). To assess long-term treatment against GORD, a cumulative treatment time of more than six months of prescribed medications was required. This was calculated using the prescribed amounts of defined daily doses, which is defined by the World Health Organisation as "the assumed average maintenance dose per day for a drug used for its main indication in adults".[120] Further, acute surgical complications were identified in the Patient Registry within 30 days of the primary surgery and reported as descriptive data. The complications identified were pneumothorax, oesophageal perforation, splenic injury, liver injury, and other specifically surgery-associated complications. The Swedish Causes of Death Registry was used to censor patients at the date of death as well as to identify patients who died within 30 days of primary laparoscopic antireflux surgery.

4.3.2.3 Statistical methods

The overall risk of reflux recurrence (requiring reoperation or medication) was visualised using Kaplan-Meier analysis. Using multivariable Cox regression the risk of recurrence was analysed and presented as hazard ratios with 95% CI. The regression models were adjusted for age at surgery (≤45, 46-60 or ≥61 years), sex, comorbidity at the date of surgery (Charlson score of 0 or ≥1), calendar year of surgery (2005-2006, 2007-2009 or 2010-2014) and total hospital volume during the study period (≤24, 25-75 or ≥76). Following the main analyses, a subgroup analysis only including individuals without comorbidities under the age of 45 was conducted.

4.3.3 Study III

4.3.3.1 Design

Systematic review and meta-analysis.

4.3.3.2 Search strategy and identification of articles

This study was a systematic review and meta-analysis assessing the available literature regarding the potential of preventing oesophageal adenocarcinoma by means of antireflux surgery. The systematic review aimed to identify all relevant studies assessing the risk of oesophageal adenocarcinoma, comparing antireflux surgery and medication due to GORD, as well as comparing antireflux surgery and the risk in the background population. The search was restricted until 12th of June 2014. PubMed/MedLine database, Web of Science, and Cochrane were searched using the following terms: oesophageal, oesophagus, neoplasm, adenocarcinoma, cancer, Barrett, fundoplication, antireflux surgery, Nissen, and reflux surgery (taking different spellings into consideration). Inclusion criteria were studies that report the incidence rates of oesophageal adenocarcinoma in surgically and medically treated patients with GORD, or compared surgically treated patients to the background population regarding the risk of oesophageal adenocarcinoma. Eligible for inclusion were cohort studies, case-control studies, and interventional studies, and no restriction regarding language was applied. Backward and forward citation tracking was also conducted to identify additional articles. To be included, the studies needed to report data regarding the number of cases and the total time of follow-up.

4.3.3.3 Statistical methods

Based on the total number of person-years and the number of cases within each group, a fixed-effects Poisson meta-analysis was conducted, resulting in pooled incidence rate ratios with 95% CI. Two separate meta-analyses were conducted: one comparing antireflux surgery with medication against GORD, and one comparing antireflux surgery with the risk in the corresponding background population. To determine statistical heterogeneity an I^2 test was conducted and the results were categorized as

low (<50%), moderate (51%-75%) or high (>75%).[121] Potential publication bias was evaluated by assessing funnel plots.

4.3.4 Study IV

4.3.4.1 Design

Nordic population-based cohort study.

4.3.4.2 The cohort and the follow-up

Based on the rapidly increasing incidence of oesophageal adenocarcinoma and the potential possibility of preventing oesophageal adenocarcinoma we conducted a multi-national cohort study to ensure the power of the analyses. By using the nationwide Patient Registries in Denmark, Finland, Iceland, Norway, and Sweden, all adult patients with a registered diagnosis of GORD were identified. This cohort was named the Nordic Antireflux Surgery Cohort (NordASCo), and details regarding the cohort have been published as a cohort profile.[122] All patients with GORD who underwent antireflux surgery were identified and were compared to patients with GORD who did not undergo such surgery, as well as the corresponding background population. The outcome was development of oesophageal adenocarcinoma, identified in the Cancer Registries, in relation to time after diagnosis or surgery. The Causes of Death Registries were used to determine date of death. The Swedish Registry of the Total Population was used to determine the incidence of oesophageal adenocarcinoma in the corresponding background population.

4.3.4.3 Statistical methods

Two statistical approaches were used. First, the risk of developing oesophageal adenocarcinoma following antireflux surgery as well as following GORD diagnosis was compared to the corresponding background population and standardized incidence ratios (SIR) with 95% CI were calculated. The incidence in the background population was derived from the Swedish population, and based on the incidence in the population of corresponding sex, age, and calendar period. The SIR were categorized based on total individual time of follow-up (<5, 5-<10, 10-<15 or ≥15 years). Second, the risk of oesophageal adenocarcinoma among the operated patients

was compared to the risk of oesophageal adenocarcinoma among the non-operated patient through Cox regression, calculating hazard ratios and 95% CI. The Cox regression models were categorized based on time after surgery or GORD diagnosis (<5, 5-<10, 10-<15 or ≥15), and adjustments were made for sex, age at follow-up (<50, 50-65 or >65 years), calendar period (-1984, 1985-1999 or 2000-), chronic obstructive pulmonary disease, and obesity or diabetes mellitus type 2. To validate the use of PPI and histamine$_2$ receptor antagonists among the patients who did not undergo antireflux surgery, the Swedish Prescribed Drug Registry was used. Based on this registry, the proportion of non-operated patients with GORD as well as severe GORD who received prescriptions during the study period was assessed.

5 RESULTS

5.1 STUDY I

Between 1997 and 2013 a total of 8,947 patients between 18 and 65 years underwent primary laparoscopic antireflux surgery in Sweden according to the Patient Registry. Main characteristics of the cohort are shown in Table 2.

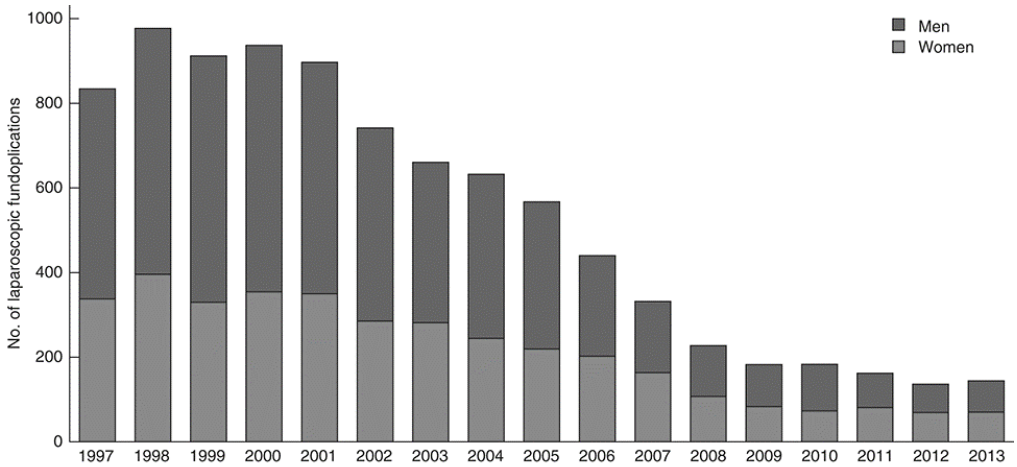
Table 2. Main characteristics of the 8,947 patients included in Study I.

	All patients Number (%)	**90-day death Number (%)**	**90-day reoperation Number (%)**
Total	8,947 (100.0)	7 (0.08)	39 (0.4)
Median age (interquartile range)	48 (38-55)	42 (41-61)	51 (39-56)
Sex			
Male	5,306 (59.3)	4 (57.1)	21 (53.9)
Female	3,641 (40.7)	3 (42.9)	18 (46.1)
Charlson comorbidity score*			
0	8,396 (93.8)	4 (57.1)	35 (89.7)
1	488 (5.5)	2 (28.6)	4 (10.3)
≥2	63 (0.7)	1 (14.3)	0 (0.0)
Median days of stay (interquartile range)	2 (1-3)	11 (3-19)	6 (3-10)

* A composite variable for quantification of general comorbid status.

When assessing the number of antireflux surgeries conducted in Sweden, a peak was seen around the year 2000 with almost 1,000 surgeries per year, followed by a steady decline, and during the last years of study, there were only approximately 150 antireflux surgeries conducted annually. This is illustrated in Figure 4. The sex distribution changed during the study period from approximately 60% male patients, to a nearly even distribution. There was an increase in the proportion of patients with severe comorbidities who underwent laparoscopic antireflux surgery. In total, there were seven deaths (0.08%) within 90 days of surgery. Compared to the entire cohort, patients who passed away within 90 days tended to have longer length of hospital-stay (Table 2). Age, year of surgery, sex or Charlson co-morbidity was not associated with any increased risk of mortality within 90 days of surgery. There were 39 reoperations (0.4%) within 90 days of primary surgery, and the reoperated group was similar with regards to age and Charlson comorbidity score as the entire cohort (Table 2). Men had a lower risk of prolonged hospital stay compared to women (odds ratio 0.76, 95% CI 0.68-0.86), and higher Charlson comorbidity score was also associated with an

increased risk of prolonged hospital stay, both among patients with Charlson comorbidity score of 1 (odds ratio 1.36, 95% CI 1.04-1.66) and 2 (odds ratio 2.27, 95% CI 1.30-4.00). In general, there was a decrease in the odds ratio of prolonged hospital stay during the study. This decrease was especially prominent during the first years of the study, and a slight increase could be seen from 2005 onwards.



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
No. of fundoplications	832	975	910	935	895	740	659	631	566	439	331	227	182	183	162	136	144
% of men	59·5	59·5	63·9	62·1	61·0	61·5	57·4	61·3	61.3	54·0	50·8	52·9	54·4	60·1	50·0	49·3	51·4
90-day reoperation	3	4	2	6	2	5	3	3	3	2	2	1	1	0	0	1	1
90-day mortality	0	1	0	0	1	0	0	0	1	0	1	0	0	1	1	1	0

Figure 4. Number of antireflux surgeries conducted in Sweden between 1997 and 2013 in the working age population, also the number of patients requiring reoperation within 90 days as well as the 90-day mortality.

5.2 STUDY II

There were 2,655 patients who underwent primary laparoscopic antireflux surgery due to GORD in the cohort, and they were followed for a mean of 5.1 years. Characteristics of the participating patients are shown in Table 3. Among the included patients, 470 (17.7%) had recurrence of reflux, defined as either receiving prescriptions of PPI of histamine$_2$ receptor antagonists for more than six months or secondary antireflux surgery. Of the patients with reflux recurrence, 393 (83.6%) were treated with medication and 77 (16.4%) underwent reoperation. Risk factors for recurrence of reflux were female sex, older age, more comorbidities, and more recent years of primary surgery, shown in Table 4. Hospital volume of antireflux surgery did not influence the risk of reflux recurrence.

Table 3. Main characteristics of the patients included in Study II.

	Entire cohort Number (%)	No recurrence of reflux Number (%)	Recurrence of reflux Number (%)
Total	2,655 (100.0)	2,185 (100.0)	470 (100.0)
Recurrence treated with			
Medication	N/A	N/A	393 (83.6)
Surgery	N/A	N/A	77 (16.4)
Sex			
Male	1,354 (51.0)	1,170 (53.5)	184 (39.1)
Female	1,301 (49.0)	1,015 (46.5)	286 (60.9)
Age			
≤45	989 (37.3)	856 (39.2)	133 (28.3)
46-60	951 (35.8)	770 (35.2)	181 (38.5)
≥61	715 (26.9)	559 (25.6)	156 (33.2)
Charlson comorbidity score*			
0	1,851 (69.7)	1,561 (71.4)	290 (61.7)
≥1	804 (30.3)	624 (28.6)	180 (38.3)

* A composite variable for quantification of general comorbid status.

Table 4. Risk factors regarding recurrence of reflux following antireflux surgery.

	Patients Number (%)	Cases of recurrence (% within each row)	Recurrence Hazard ratio (95% CI)*
Sex			
Male	1,354 (51.0)	184 (13.6)	1.00 (Reference)
Female	1,301 (49.0)	286 (22.0)	1.57 (1.29-1.90)
Age (years)			
≤45	989 (37.3)	133 (13.4)	1.00 (Reference)
46-60	951 (35.8)	181 (19.0)	1.28 (1.02-1.61)
≥61	715 (26.9)	156 (21.8)	1.41 (1.10-1.81)
Charlson comorbidity score**			
0	1,851 (69.7)	290 (15.7)	1.00 (Reference)
≥1	804 (30.3)	180 (22.4)	1.36 (1.13-1.65)
Year of surgery			
2005-2006	1,098 (41.4)	177 (16.1)	1.00 (Reference)
2007-2009	802 (30.2)	146 (18.2)	1.61 (1.27-2.03)
2010-2014	755 (28.4)	147 (19.5)	3.86 (2.98-5.02)
Hospital volume			
≤24	266 (10.0)	38 (14.3)	1.00 (Reference)
25-75	863 (32.5)	161 (18.7)	1.13 (0.79-1.62)
≥76	1,526 (57.5)	271 (17.8)	1.09 (0.77-1.53)

* Hazard ratio and 95% confidence interval.

** A composite variable for quantification of general comorbid status.

In a separate analysis only including 799 patients aged 45 years or younger with no co-morbidities, 11.1% of the men and 17.1% of the women had recurrence of reflux. Compared to the rest of the population, the risk of recurrence was decreased both among men (hazard ratio 0.66, 95% CI 0.49-0.90) and women (hazard ratio 0.67, 95% CI 0.48-0.93). In the cohort, 109 (4.1%) had any complication within 30 days of

antireflux surgery. The most common complications were infections (1.1%), bleeding (0.9%) and oesophageal perforation (0.9%). After primary antireflux surgery, 21 patients (0.8%) received a diagnosis of dysphagia during the study period, and 14 of these patients (0.5%) required endoscopic dilatation. Following secondary antireflux surgery, 18 patients (23.4%) suffered from a complication, and the most frequent were infection (6.5%), oesophageal perforation (6.5%) and bleeding (5.2%).

5.3 STUDY III

Following the systematic search of PubMed/MedLine, Web of Science and Cochrane, 1,987 studies were considered for inclusion in this systematic review, and among these 12 met the inclusion criteria, shown in the search strategy in Figure 5.

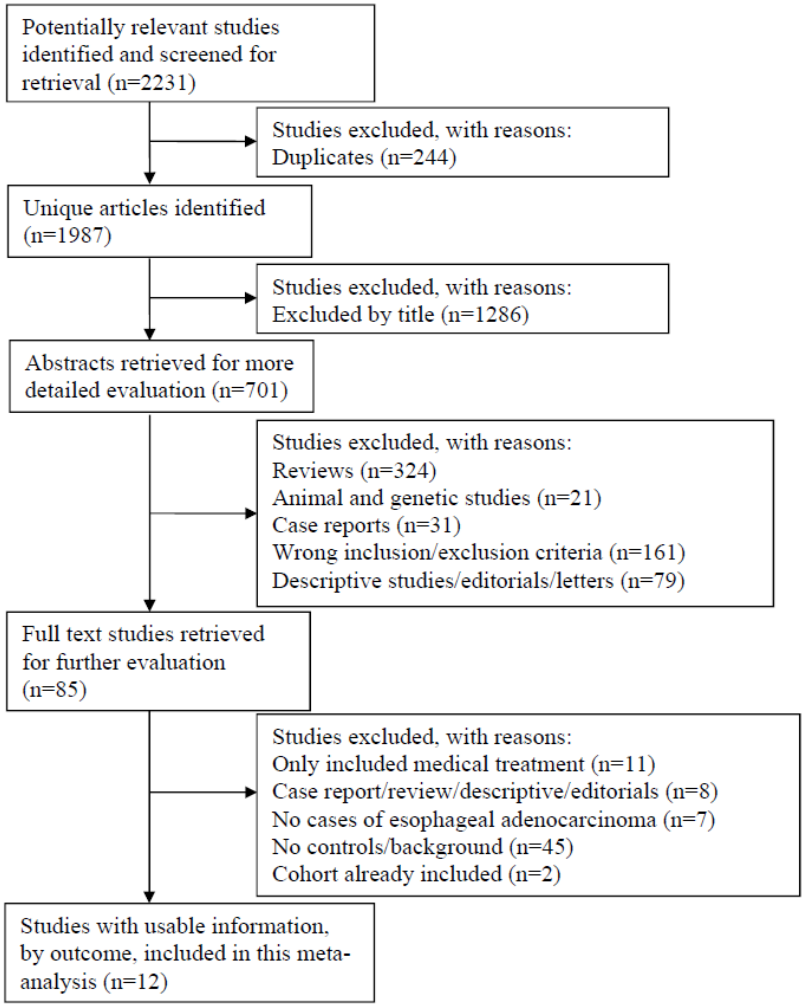


Figure 5. Search strategy used in Study III, and number of eligible studies.

Ten studies compared an operated to a non-operated group of patients, and these were from Ireland, Spain, Sweden, the United Kingdom, and the United States. In total there were 100,479 patient-years following antireflux surgery, and 403,459 person-years among patients with reflux who did not undergo such surgery. The meta-analysis of these ten studies comparing antireflux surgery with medication found an overall incidence rate ratio of 0.89 (95% CI 0.66-1.19; I^2 0%), shown in Figure 6. A meta-analysis only including patients with a known diagnosis of Barrett's oesophagus indicated a decreased risk of oesophageal adenocarcinoma in the antireflux surgery group (incidence rate ratio 0.46 (95% CI 0.20-1.08). In an analysis only including patients without Barrett's oesophagus or with unknown diagnosis the corresponding incidence rate ratio was 0.98 (95% CI 0.72-1.33).

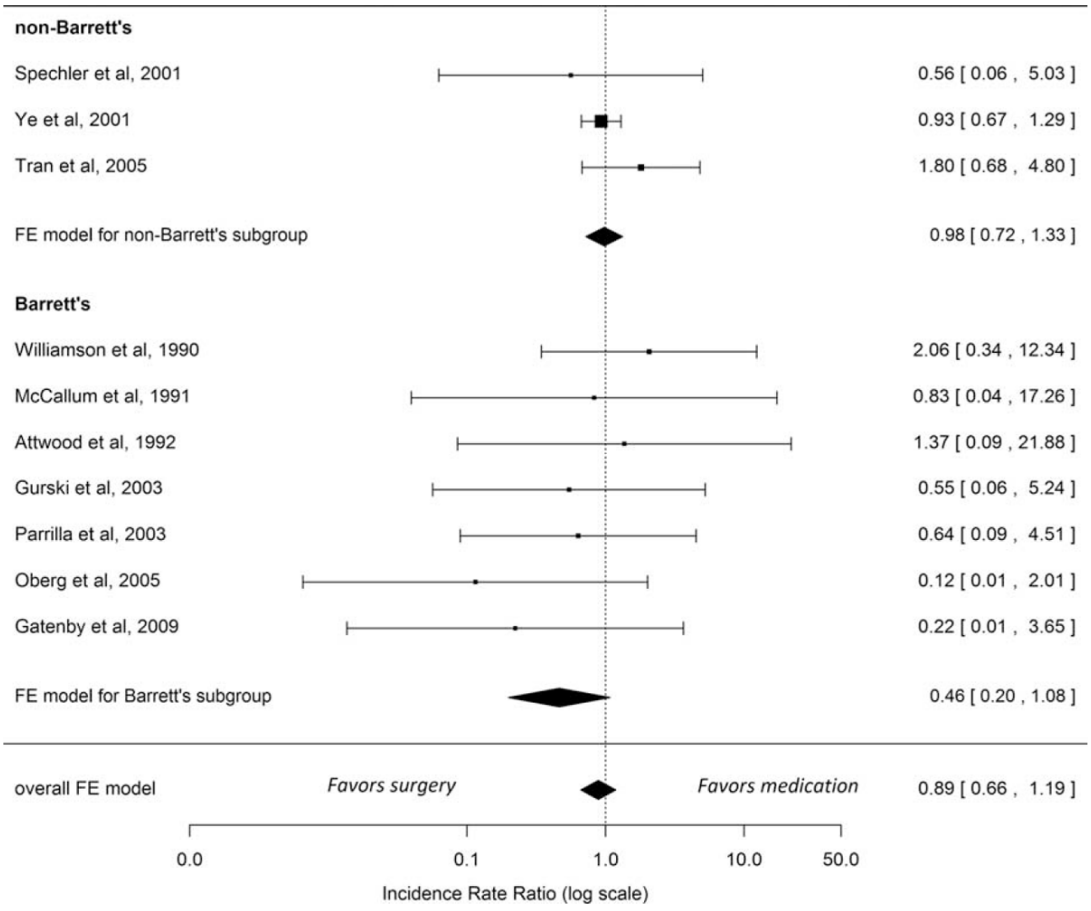


Figure 6. Forrest plot comparing the risk of oesophageal adenocarcinoma following antireflux surgery to medication, among patients with and without Barrett's oesophagus, as well as overall.

Two studies compared the risk of oesophageal adenocarcinoma in patients who underwent antireflux surgery to the risk in the general background population, one conducted in Finland and one in Sweden. These included 134,438 and 120,514

person-years, respectively. The meta-analysis of these studies (Figure 7) found an incidence rate ratio of 10.78 (95% CI 8.48-13.71) compared to the general background population.

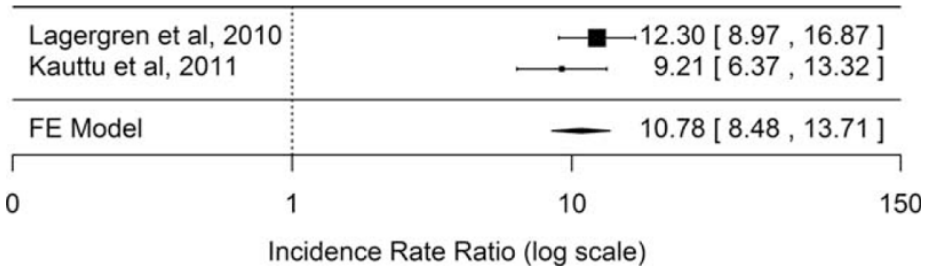


Figure 7. Forrest plot comparing the risk of oesophageal adenocarcinoma following antireflux surgery to the general background population.

5.4 STUDY IV

In study IV, the entire study cohort included 942,906 patients with GORD in the five Nordic countries. Among these, 48,414 patients had undergone antireflux surgery, including 30,537 patients with a diagnosis of severe GORD. Some characteristics of the study participants are presented in Table 5. Among the patients with GORD who did not undergo antireflux surgery, 2,368 patients (0.3%) subsequently developed oesophageal adenocarcinoma at a median age of 71 years, and the vast majority of these were men (79.6%). Among the patients with severe GORD who did not undergo antireflux surgery 1,351 patients (0.5%) later developed oesophageal adenocarcinoma at a median age of 70 years, and with an even more pronounced overweight of men (83.3%). Among the patients in the overall GORD group who underwent antireflux surgery 177 patients (0.4%), of which 86.4% were men, developed oesophageal adenocarcinoma during the study period, at a median age of 66 years. Among the patients with severe GORD who underwent antireflux surgery, 149 (0.5%) developed oesophageal adenocarcinoma, at a median age of 65 years, and among who 85.9% were men. Within the group of patients with GORD who did not undergo antireflux surgery, the validation analysis found that 92.1% were users of PPI or histamine$_2$ receptor antagonists. The corresponding figure among patients with severe GORD who did not undergo antireflux surgery was 97.3%.

Table 5. Main characteristics of the patients included in Study IV.

Gastro-oesophageal reflux disease		
	No antireflux surgery Number (%)	**Antireflux surgery Number (%)**
Total		
Patients	894,492 (100)	48,414 (100)
Person-years of follow-up	6,511,385 (100)	617,181 (100)
Sex		
Male	434,035 (48.6)	27,161 (56.1)
Female	459,340 (51.4)	21,253 (43.9)
Age		
<50 years	291,732 (32.6)	23,825 (49.2)
50-65 years	267,861 (29.9)	18,206 (37.6)
>65 years	334,899 (37.4)	6,383 (13.2)
Oesophageal adenocarcinoma	2,368 (0.3)	177 (0.4)
Median age at diagnosis (interquartile range)	71.0 (62.0-78.0)	66.0 (58.0-73.0)
Males	1,884 (79.6)	153 (86.4)
Females	484 (20.4)	24 (13.6)

Severe gastro-oesophageal reflux disease		
	No antireflux surgery Number (%)	**Antireflux surgery Number (%)**
Total		
Patients	264,543 (100)	30,537 (100)
Person-years of follow-up	2,496,630 (100)	391,908 (100)
Sex		
Male	146,502 (55.4)	17,756 (58.1)
Female	118,041 (44.6)	12,781 (41.9)
Age		
<50 years	83,419 (31.5)	15,529 (50.9)
50-65 years	82,703 (31.3)	11,686 (38.3)
>65 years	98,421 (37.2)	3,322 (10.9)
Oesophageal adenocarcinoma	1,351 (0.5)	149 (0.5)
Median age at diagnosis (interquartile range)	70.0 (62.0-77.0)	65.0 (58.0-73.0)
Males	1,125 (83.3)	128 (85.9)
Females	226 (16.7)	21 (14.1)

The comparison of patients with GORD and severe GORD to the corresponding background population are shown in Table 6. Among patients with GORD who underwent antireflux surgery, the SIR decreased from 39.19 (95% CI 28.79-52.11) <5 years after surgery to 1.34 (95% CI 0.98-1.80) ≥15 years after surgery. A similar pattern was seen for patients with severe GORD who underwent antireflux surgery, although from a higher initial level; the SIR decreased from 72.28 (95% CI 52.08-97.70) <5 years after surgery to 1.67 (95% CI 1.15-2.35) ≥15 years after surgery. Among patients with GORD who did not undergo antireflux surgery (i.e. medically treated), the SIR decreased from 17.71 (95% CI 16.88-18.56) <5 years after inclusion

to 0.69 (95% CI 0.59-0.81) ≥15 years after inclusion. Among patients with severe GORD who did not undergo antireflux surgery, the SIR decreased from 37.65 (95% CI 35.20-40.22) <5 years after inclusion to 1.16 (95% CI 0.97-1.39) ≥15 years after inclusion.

Table 6. Risk of oesophageal adenocarcinoma (OAC) among patients with gastro-oesophageal reflux disease (GORD) and severe GORD following antireflux surgery or not, compared to the corresponding background population.

Gastro-oesophageal reflux disease						
	No antireflux surgery			**Antireflux surgery**		
	Patients	OAC	SIR (95% CI)*	Patients	OAC	SIR (95% CI)*
Follow-up (years)						
<5	438,096	1,717	17.71 (16.88-18.56)	7,376	47	39.19 (28.79-52.11)
5-<10	223,842	310	2.06 (1.83-2.30)	10,068	39	7.63 (5.42-10.43)
10-<15	127,960	185	1.31 (1.12-1.51)	13,428	46	3.64 (2.66-4.85)
≥15	104,594	156	0.69 (0.59-0.81)	17,542	45	1.34 (0.98-1.80)
Severe gastro-oesophageal reflux disease						
	No antireflux surgery			**Antireflux surgery**		
	Patients	OAC	SIR (95% CI)*	Patients	OAC	SIR (95% CI)*
Follow-up (years)						
<5	94,840	882	37.65 (35.20-40.22)	3,546	42	72.28 (52.08-97.70)
5-<10	70,790	216	3.90 (3.40-4.45)	6,632	34	10.08 (6.98-14.09)
10-<15	50,475	130	2.02 (1.68-2.39)	9,494	40	4.47 (3.20-6.09)
≥15	48,351	123	1.16 (0.97-1.39)	10,865	33	1.67 (1.15-2.35)

* Standardised incidence ratio and 95% confidence interval

The analysis comparing patients with GORD who had undergone antireflux surgery to patients with GORD who had not undergone such surgery is presented in Table 7. Compared to patients with GORD who did not undergo antireflux surgery, patients who underwent such surgery were at a stable elevated risk of oesophageal adenocarcinoma <5 years and ≥15 years after surgery (hazard ratio 1.86, 95% CI 1.39-2.49, and 1.80, 95% CI 1.28-2.54, respectively). In the group with severe GORD, the hazard ratio also remained stable, but elevated, among the patients who underwent surgery compared to the patients who did not undergo such surgery, with a hazard ratio of 1.62 (95% CI 1.18-2.22) <5 years after surgery and 1.69 (95% CI 1.14-2.51) ≥15 years after surgery.

Table 7. The risk of oesophageal adenocarcinoma (OAC) among patients with GORD and severe GORD comparing patients who have underwent antireflux surgery or not.

Gastro-oesophageal reflux disease						
	No antireflux surgery			**Antireflux surgery**		
	Total	OAC	Hazard ratio (95% CI)*	Total	OAC	Hazard ratio (95% CI)*
Follow-up (years)						
<5	438,096	1,717	1.00 (Reference)	7,376	47	1.86 (1.39-2.49)
5-<10	223,842	310	1.00 (Reference)	10,068	39	2.02 (1.44-2.84)
10-<15	127,960	185	1.00 (Reference)	13,428	46	1.96 (1.41-2.74)
≥15	104,594	156	1.00 (Reference)	17,542	45	1.80 (1.28-2.54)
Severe gastro-oesophageal reflux disease						
	No antireflux surgery			**Antireflux surgery**		
	Total	OAC	Hazard ratio (95% CI)*	Total	OAC	Hazard ratio (95% CI)*
Follow-up (years)						
<5	94,840	882	1.00 (Reference)	3,546	42	1.62 (1.18-2.22)
5-<10	70,790	216	1.00 (Reference)	6,632	34	1.81 (1.24-2.63)
10-<15	50,475	130	1.00 (Reference)	9,494	40	1.71 (1.18-2.49)
≥15	48,351	123	1.00 (Reference)	10,865	33	1.69 (1.14-2.51)

* Hazard ratio and 95% confidence interval

6 METHODOLOGICAL CONSIDERATIONS

In the current thesis, three of the studies are cohort studies and one is a systematic review and meta-analysis. These designs have different methodological challenges.

6.1 COHORT STUDIES

Study I, II, and IV are population-based cohort studies. Two (Study I and II) were nationwide Swedish studies and one (Study IV) included nationwide data from all five Nordic countries. A cohort study consists of a designated group of individuals with information about one or more pre-specified exposures who are followed up over a period of time for one or more outcomes of interest.[123] Due to the similarities in study design in studies I, II, and IV they share some methodological aspects. A major strength is the population-based design, including virtually all patients in Sweden or the Nordic countries who fulfil the inclusion criteria and with complete follow-up in the registries. This design counteracts selection bias and loss to follow-up. The nationwide inclusion also enabled large sample sizes, which allowed the study of the rare outcome oesophageal adenocarcinoma with sufficient power. Based on the richness of data in the included registries, it is also possible to adjust the results for potential confounding factors. Among weaknesses with observational study designs in general is the risk of different types of systematic errors (bias), which might affect the validity of the study. There are three types of bias that might affect an observational study: selection bias, information bias, and confounding. The ambition when designing any observational study is to reduce such biases, thereby reducing the systematic errors.

Selection bias constitutes a systematic non-random error in the selection and inclusion of individuals in the study which might result in the studied cohort not reflecting the population that is intended to be analysed.[123] Since all cohort studies included in this thesis are population-based, virtually including all patients within each country, selection bias should not be affected due to lack of participation. However, there is a risk that the definitions regarding the inclusion criteria might affect the participation. Further, there is a risk that local traditions within different hospitals or clinics might influence the diagnoses that patients receive. This might for example influence what

patients receive a diagnosis of heartburn or not in a clinical practice if this is not the main reason for the patient seeking medical care.

Information bias is a "flaw in measuring exposure, covariate, or outcome variables that results in different quality of information between comparison groups".[124] It can be categorized as differential (non-random) when the misclassification differs between the comparison groups or non-differential (random) when the misclassification does not differ between the groups. Non-differential misclassification is often considered to lead to an underestimation of associations. In the current studies, misclassification should not be a major issue if the validity of the codes that are used is high. Since diagnostic and surgical codes often are directly associated to monetary reimbursement for the clinics, the validity of these is generally high. The cancer diagnoses are often reported centrally directly from the pathologists or oncological clinics, which also results in a high reliability of the coding. In study II, medications in the Prescribed Drug Registry were used as a proxy for recurrence of GORD, however it is impossible to know the compliance, i.e. whether the patients actually took their medication or not, based on this data. To avoid bias due to this, we decided to only include patients who received prescriptions accounting for at least six months of medication.

Confounding constitutes a challenge in most observational research. A confounder is defined as a factor which is associated both with the exposure and outcome, without being in the causal pathway between these two. In the studies included in this thesis, mainly multivariable regression was used to handle confounding. Although confounding was attempted to be handled within each study there is always a risk of residual confounding of unknown factors and rough categorisation of factors adjusted for, which might affect the analyses. This might also be caused by low registration of factors that are considered confounders or a lack of a good enough proxy that might reflect such confounding.

Random error is the variation of test results when repeated. These random errors might be present in any study. However, depending mainly on sample size, the level of precision can be increased, thereby resulting in more reliable results. Any analysis results in a point estimate, but to give a measurement of the precision of the analysis these are often presented with 95% confidence intervals or a p-value. The confidence

interval reflects within which interval a certain proportion of the measurements (e.g. 95%) would fall in if the measurements were conducted numerous times (and was free from bias). Another common measurement which indirectly reflects the precision is the *p*-value. *P*-value is a measurement of the probability that the null hypothesis is true, meaning that there is no association between the exposure and the outcome. Therefore, a low *p*-value would indicate evidence against the null hypothesis, meaning that the alternative hypothesis is true, suggesting a true difference between the two groups that are compared. In clinical studies 95% confidence intervals are often more informative by not only providing information regarding statistical significance, but also regarding direction and strength of the effect.[125]

6.2 SYSTEMATIC REVIEW AND META-ANALYSIS

Study III is a systematic review and meta-analysis. Based on a systematic search in three of the major databases for scientific literature (PubMed/MedLine database, Web of Science, and Cochrane) relevant articles were identified. Following this, data were extracted and analysed in a meta-analysis. Meta-analysis can be a powerful tool to summarize large amounts of data, and reach new, more reliable conclusions. There are however many challenges with this approach as well. Except for the potential biases involved in each of the included studies, there are specific issues related to meta-analyses: publication bias, search bias, selection bias and heterogeneity.

Publication bias represents one of the major issues both in meta-analyses and in the medical literature in general. This represents the issue that positive results of statistical significance and results with a larger "media impact" are more likely to be published and to be published more rapidly than negative or inconclusive results.[126,127] This bias will directly affect the data available for inclusion in a meta-analysis. Due to the nature of the issue where many studies are initiated without being centrally registered or followed up, it is hard to assess how large the issue is. One method of determining whether publication bias exists is to conduct a funnel plot. A funnel plot is a scatterplot with the treatment effect on the x-axis and the standard error (study precision or random error) on the y-axis, thereby large studies will appear at the top of the funnel with smaller studies at the bottom. The dotted lines represent the assumed 95% confidence interval around the treatment effect and an asymmetrical distribution

indicates publication bias. The funnel plot of the main analysis in study IV is presented in Figure 8. In the current meta-analysis, the overall assessment is that no significant publication bias exists, although there is a slight skewness among the smallest studies.

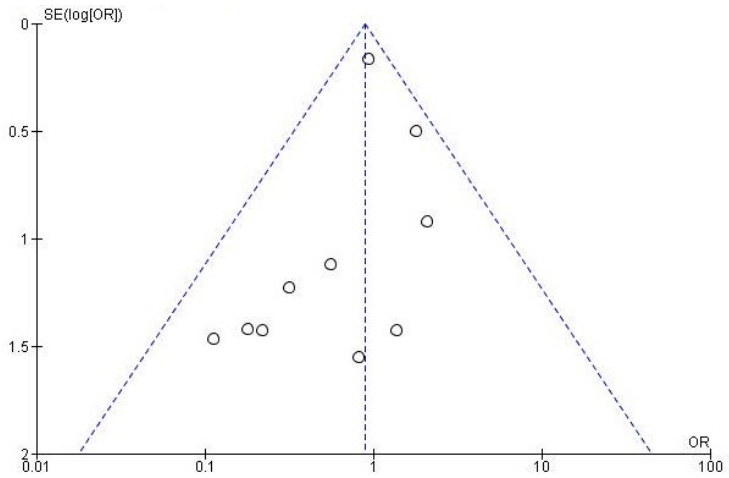


Figure 8. Funnel plot of the included articles in study IV comparing patients undergoing surgery to patients receiving medical treatment.

Search bias represents the issues that can arise from a skewed or incomplete search. This can either be due to the selection of keywords used or the selection of databases to search. If the search strategy is too narrow or incomplete, important studies might be missed, thereby resulting in a bias in the meta-analysis.

Selection bias in a meta-analysis may occur during the selection and inclusion of studies following the search. To ensure that the selection takes place in a controlled and reproducible way, inclusion criteria need to be determined beforehand and strictly followed. These criteria should state what type of study designs that will be included, what kind of outcome measurements are necessary, et cetera. This was done in study III.

Statistical heterogeneity is a measurement of the variation in the studies, which helps determine if the studies are similar enough to be combined in a meta-analysis. One method of determining statistical heterogeneity is by calculating I^2 which measures the percentage of variance that can be attributed to study heterogeneity, which was used in the current meta-analysis. If the heterogeneity is determined to be low, a fixed

effects meta-analysis can be conducted, in which each of the included studies are assumed to estimate the same underlying parameter, and that the different estimates between the studies are only due to random error. If the heterogeneity is found to be large, this can be handled using a random effects meta-analysis, which assumes that the effects studied are not identical, both due to heterogeneity between the studies and due to random error within each study.

Clinical heterogeneity can also affect the conduction and interpretation of a meta-analysis. If the included studies are conducted in very different clinical settings, where for example the indication for treatment, type of treatment, follow-up, and duration of treatment are very different, the clinical heterogeneity might affect the reliability and possibility to interpret the results of the meta-analysis.

7 GENERAL DISCUSSION

7.1 STUDY I

Study I found very low mortality and reoperation rates among adults of working age who underwent primary laparoscopic antireflux surgery. The trend in the number of surgeries showed a clear peak around the turn of the millennium, followed by a steady decrease. The proportion of patients with severe comorbidities who underwent laparoscopic antireflux surgery increased during the later years.

Strengths in the study are the complete coverage of the registries as well as the complete follow-up of the patients. Among weaknesses is the risk that patients who are selected for surgery might be healthier compared to the general population. However, such selection bias still reflects clinical practice due to the population-based methodology. There is also a risk of confounding due to potential confounders such as tobacco smoking, which might affect the outcomes.

Due to the low risk of mortality and reoperation, laparoscopic antireflux surgery can be considered a safe procedure, with a risk similar to other operations for benign conditions. The initial increase in the number of surgeries might both be attributable to an increased detailed coding following the implementation of the NOMESCO as well as an actual increase in the number of procedures. The shown decrease in the number of surgeries can be attributed to a few different factors. The introduction and increased availability and use of PPI during the late 20th century had a large impact on the pharmacological treatment options for GORD.[128] Since PPI generally offer good symptom relief for most patients, this is indeed the main treatment option. Further, the potential risks of surgical complications and mortality might have affected clinicians' willingness to refer patients to surgery, especially in relation to the safer and effective pharmacological treatment option, and similar patterns in the use of surgery have been shown in previous studies.[129] Some recent studies have however raised the question regarding side-effects due to long-term treatment with PPI.[34-37] There is also a matter of availability of surgery and monetary reimbursement, which can affect the possibility to undergo antireflux surgery. The aspect of cost-effectiveness was not assessed in the current study. However surgery might be a more cost-effective

treatment option in the long-term setting, making it an appealing treatment option especially for young patients.[54]

The study also found an increased risk of prolonged hospital stay associated with more comorbidities and higher age. This might be due to a higher risk of complications as well as a slower recovery following surgery.

Overall, laparoscopic antireflux surgery can be considered a safe treatment option for GORD.

7.2 STUDY II

In study II we found that among adult patients undergoing primary laparoscopic antireflux surgery, 17.7% had recurrence of reflux, defined as either undergoing reoperation or receiving medical treatment (PPI or histamine$_2$ receptor antagonists) for more than six months. Higher risk of recurrence was associated with female sex, older age, and comorbidities. The number of surgeries performed at the hospital was not associated with increased risk of recurrence. The lowest risk of recurrence was found among young and otherwise healthy men, and in a sub-analysis of patients below 45 years of age and without comorbidities we found a recurrence rate of 11.1% among men. The overall risk of recurrence in the study is lower than most previously published cohort studies on the topic,[130-135] and the proportion of patients undergoing reoperation was also lower than previous studies.[49,50]

Among the strengths of the current study is the nationwide and complete coverage. Further, the combined outcome, both including reoperation and long-term medication reliably identifies patients with recurrence. Some of the weaknesses is the use of PPI bought over the counter which is not included in the registry and whether or not patient compliance was sufficient. Clinical practice might also vary between clinics, inducing an uncertainty in the coding. Further, as in any observational study, the risk of confounding is a challenge in the current study.

The explanation for the findings might be attributed both to the study design, patient selection, as well as biological aspects. The study design was a nationwide study with complete follow-up and a larger cohort compared to most previously published cohort

studies. Further, due to the increasing use of medication against GORD and decreasing use of surgery over the last decades, the selection of patients might be stricter and the surgical quality at the centres that conduct the surgeries might be higher. However, there is a risk that patients who are eventually selected for surgery suffer from more severe GORD with incomplete relief of symptoms following medication. Considering this, the rate of recurrence in the study might be considered to be low. Some previous studies have shown that women might experience more severe symptoms of GORD despite having an objectively similar grade of GORD as men.[136] Age and comorbidities might be associated with a higher risk of recurrence due to a more severe and refractory type of GORD, which might be at a higher risk of recurrence.

The study also assessed complications within 30 days of primary and secondary antireflux surgery and showed a complication rate of 4.1% and 23.4%, respectively. The most common complications were infection, bleeding and oesophageal perforation. Previous studies have found low, albeit higher than ours, risk of complications. The higher risk of complications associated with secondary surgery compared to primary surgery is in line with previously published data, further highlighting the risk of complications following reoperation.[137,138]

In conclusion, the risk of recurrence following laparoscopic antireflux surgery is relatively low, particularly in young men, as is the risk for complications following the procedure. Therefore, antireflux surgery might be an underused treatment option.

7.3 STUDY III

The systematic review and meta-analysis in study III did not find a more preventive effect against the development of oesophageal adenocarcinoma following antireflux surgery compared to antireflux medication in the overall analysis. However, there was a lower point estimate in favour of surgery in the meta-analysis only including patients with Barrett's oesophagus compared to the analysis only including patients without confirmed Barrett's oesophagus. In the analysis comparing antireflux surgery to the general background population, the risk of oesophageal adenocarcinoma remained highly elevated over time following surgery.

One limitation of a meta-analysis is the weaknesses associated with the individual studies. For example, none of the included studies differentiated between duration of GORD and symptom severity (although the diagnosis of Barrett's oesophagus was included in some studies). Further, no analysis was based on the duration of treatment, i.e. time after surgery or initiation of medication. There is also a risk of search and selection bias. Similar to any meta-analysis, there is also a risk of publication bias (the file drawer problem) meaning that non-significant or negative results might not have been published in the first place, making such studies impossible to identify and include in the analysis.

In conclusion, this study did not find any significant difference between antireflux surgery and medication regarding prevention of oesophageal adenocarcinoma. There was, however, a lower point estimate favouring surgery among patients with Barrett's oesophagus. This could indicate that patients with Barrett's oesophagus might benefit more from antireflux surgery, although the data available is not sufficient to establish this.

7.4 STUDY IV

This nationwide Nordic study found a decreasing risk of developing oesophageal adenocarcinoma compared to that of the general background population over time, both among patients undergoing surgery and patients assumed to receive medical treatment. When comparing these two groups, no trend was seen over time, and the patients who underwent surgery remained at a constant, slightly elevated level.

Strengths include the population-based design, reflecting clinical practice and facilitating generalisability, and large cohort size, increasing the statistical power. The separate analyses of overall GORD as well as severe GORD enabled a valuable comparison between these two groups. Among the weaknesses were the risk of residual confounding and incomplete data regarding medical consumption in the groups.

Previous studies have not found any preventive effect following antireflux surgery compared to the background population, both separately and when combined in a meta-analysis (Study III).[139-141] This might be attributable to earlier studies only

including few cases, with a small number of patients included in the longer follow-up categories. In the current study, there was no change in risk over time comparing the surgically treated and presumed medically treated patients. However, patients who underwent surgery were generally at a higher risk of oesophageal adenocarcinoma. This could be due to patients undergoing surgery might have had more severe GORD with longer duration before initiation of treatment.[142]

In conclusion, effective treatment of GORD with surgery or medication seems to decrease the risk of developing oesophageal adenocarcinoma over time, with a risk on the same level as the background population more than 15 years after surgery or diagnosis. Medical and surgical treatment seems to follow the same pattern of decreasing risk of oesophageal adenocarcinoma over time.

7.5 CLINICAL IMPLEMENTATIONS

In a clinical setting, this thesis concludes that laparoscopic antireflux surgery can be considered a safe procedure with low postoperative mortality and few complications. Laparoscopic antireflux surgery is also associated with a short postoperative hospital stay and a low risk of recurrence of reflux, especially among young and healthy individuals. Previous studies have found that both overall health-related quality of life as well as the GORD-specific quality of life is improved following antireflux surgery, comparing patients undergoing surgery and receiving medical treatment.[43] There are also studies indicating that surgical treatment of GORD might be more cost-effective than medication, especially in a long-term setting compared to medical treatment.[43,143,144]

Medication, on the other hand, is easily available, both over the counter and on prescription, and it carries few direct side effects. However, some studies have raised concerns that long-term treatment with PPI might lead to adverse events, such as hip fracture, *Clostridium difficile*-associated diarrhoea, and community-acquired pneumonia.[34-37] Further, recent studies have also raised concerns regarding long-term medication using PPI and risk of gastric cancer.[38,39]

The thesis also showed that effective treatment against GORD can reduce the risk of developing oesophageal adenocarcinoma over time, with a risk at the same level as

the background population after more than 15 years. In all, this would mean that a low-risk procedure, with low mortality and morbidity, could decrease the risk of developing a highly lethal cancer with poor outcome and increasing incidence. In parallel with this, the number of individuals undergoing laparoscopic antireflux surgery has drastically decreased, reaching its lowest levels during the last few years.

In summary, first-line treatment of GORD should continue to be medication with PPI. However, surgical treatment against GORD using laparoscopic antireflux surgery is likely an underused treatment option in clinical practice today and should remain in the clinical arsenal. Surgery should especially be considered among young and healthy individuals with severe GORD, who otherwise would require long-term medical treatment for a potentially life-long period of time.

8 CONCLUSIONS

- The short-term postoperative risks associated with laparoscopic antireflux surgery are low, regarding both complications and mortality.
- The rate of recurrence of reflux following antireflux surgery is rather low in a long-term setting, particularly in younger and otherwise healthy men.
- Effective treatment with surgery or medication against GORD seems to prevent oesophageal adenocarcinoma; antireflux surgery and medication are seemingly similarly effective in this respect.

9 FUTURE RESEARCH

GORD is common in the western population with an increasing incidence. Regarding the use of laparoscopic antireflux surgery as a treatment of GORD, future research should focus on identifying which patients should be recommended such surgery, both in relation to associated risks and clinical relieve of reflux symptoms. Further, future research should aim at determining whether the presence of Barrett's oesophagus influences what treatment is most beneficial and should be recommended. Another aspect is to clarify which treatment is most cost-effective in a long-term clinical setting, and whether this might affect the choice of treatment. From a pharmacological perspective, large population-based studies should also aim at further determining the potential long-term side effects of PPI, and further elucidate how to handle patients requiring long-term medical treatment.

Future research should also aim at the oncopreventive aspects following antireflux surgery, especially regarding oesophageal adenocarcinoma. This thesis provides some evidence of an oncopreventive effect following treatment of GORD, but this needs to be established in further research and due to the low incidence of oesophageal adenocarcinoma large studies with long duration of follow-up are needed. Further, GORD has been indicated to be associated with some extra-oesophageal cancers, such as laryngeal and pharyngeal cancers, and these should also be studied in relation to antireflux surgery.

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

10.1 BAKGRUND

Gastroesofageal refluxsjukdom orsakas av läckage av surt maginnehåll förbi den övre magmunnen och upp i matstrupen, vilket leder till halsbränna och/eller sura uppstötningar. Det uppskattas att 10-20% av den vuxna befolkningen lider av gastroesofageal refluxsjukdom, och denna siffra har ökat senaste decennierna. Långvarig gastroesofageal refluxsjukdom kan leda till inflammation i matstrupen (esofagit), cellförändringar i matstrupen (Barretts esofagus), men även matstrupscancer (esofagusadenocarcinom). Matstrupscancer är en cancer som ökar i västvärlden och är associerad med krävande behandling, men har trots det en dyster prognos. Gastroesofageal refluxsjukdom kan antingen behandlas med läkemedel, och då framförallt protonpumpshämmare som verkar genom att minska syraproduktionen i magsäcken och därmed symtomen, eller kirurgiskt med antirefluxkirurgi. Vid antirefluxkirurgi förs en del av magsäcken runt matstrupen och sys ihop på framsidan, vilket leder till att den övre magmunnen snävas åt vilket mekaniskt hindrar maginnehållet från att nå matstrupen.

Denna avhandling syftar till att klargöra riskerna vid antirefluxkirurgi, förtydliga risken att återfå symtom av reflux efter antirefluxkirurgi, samt utreda möjligheten att förhindra matstrupscancer genom effektiv behandling av gastroesofageal refluxsjukdom.

10.2 METODER OCH RESULTAT

Tidigare studier har visat att risken för allvarliga komplikationer och död i samband med antirefluxkirurgi med titthålsteknik varit relativt hög, och likaså risken att patienterna ska få tillbaka sina refluxbesvär efter operationen.

Syftet med **Studie I** var att kartlägga risken för död, behov av en akut omoperation, samt risken för förlängd sjukhusvistelse efter antirefluxkirurgi hos patienter mellan 18 och 65 års ålder. Patienterna identifierades i patientregistret och följdes upp i både Patientregistret samt Dödsorsaksregistret, Populationsregistret användes för att beräkna trender avseende antirefluxkirurgi. Studieperioden var från 1997 till 2013.

Multivariabel logistisk regressionsanalys justerat för ålder, kön, år för operation, och samsjuklighet användes för att identifiera riskfaktorer för omoperation eller förlängd sjukhusvistelse. Totalt inkluderades 8 947 patienter i studien. Studien fann en mycket låg risk för död (0,08%) och omoperation (0,4%) inom 90 dagar efter antirefluxkirurgi som utförts med titthålsteknik. Vidare visade studien att antalet operationer som utförs i Sverige radikalt minskade under studietiden, från 15,3 per 100 000 invånare 1997 till 2,4 per 100 000 invånare 2013. Under samma period observerades att andelen patienter med tung samsjuklighet ökat, men denna ökning i samsjuklighet åtföljdes dock inte av någon ökning i dödlighet eller omoperation.

Syftet med **Studie II** var att undersöka hur stor andel av patienterna som fick tillbaka sina refluxbesvär bland de vuxna patienter som genomgått antirefluxkirurgi med titthålsteknik. Studien var en kohortstudie mellan åren 2005 och 2014, och patienterna identifierades i Patientregistret, vilket länkades till Dödsorsaksregistret samt Läkemedelsregistret. Som mått på återfall av refluxbesvär användes antingen operation med förnyad antirefluxkirurgi eller medicinsk behandling av gastroesofageal refluxsjukdom som patienten erhållit recept på och vilken översteg sex månaders behandlingstid. Multivariabel Cox regression justerat för ålder, kön, år för operationen, samsjuklighet, samt antalet operationer som utförts på sjukhuset användes för att identifiera riskfaktorer för att patienten skulle återfå behandlingskrävande refluxbesvär efter operation. Vidare undersöktes risken att drabbas av komplikationer i samband med den primära operationen eller en eventuell omoperation. Totalt inkluderades 2 655 patienter, och dessa följdes under 5,1 års tid (medelvärde). Av patienterna drabbades 17,7% av behandlingskrävande refluxbesvär efter antirefluxkirurgi, som antingen behandlades medicinskt eller kirurgiskt. Majoriteten av dessa (83,6%) behandlades med läkemedel. Riskfaktorer för att återfå besvär efter antirefluxoperation var kvinnligt kön, högre ålder, samsjuklighet, samt senare operationsår, men risken var särskilt låg hos unga och i övrigt friska män. Något samband mellan antalet operationer och risken att återfå behandlingskrävande refluxbesvär kunde inte ses. Bland de som genomgick antirefluxkirurgi med titthålsteknik drabbades 4,1% av en komplikation inom 30 dagar efter operationen, motsvarande siffra vid omoperation var 23,4%. De vanligaste komplikationerna var infektion, blödning, och skador på matstrupen.

Syftet med **Studie III** var att identifiera publicerade artiklar som utvärderat möjligheten att förhindra utvecklingen av matstrupscancer genom behandling av gastroesofageal refluxsjukdom, och genom en meta-analys väga samman dessa resultat. Tre stora internationella databaser söktes igenom, och totalt identifierades 12 artiklar som antingen jämförde kirurgisk och medicinsk behandling, eller kirurgisk behandling med bakgrundbefolkningen. Tio studier jämförde medicinsk och kirurgisk behandling, och vid sammanvägd analys av dessa kunde ingen skillnad mellan medicinsk och kirurgisk behandling påvisas. Vid separata analyser mellan de studier som bara inkluderade patienter med Barretts esofagus och de som inte gjorde detta sågs en antytt mer skyddande effekt av kirurgi, även om någon statistiskt säkerställd skillnad inte gick att påvisa. Två studier jämförde risken för matstrupscancer efter antirefluxoperation med risken hos bakgrundsbefolkningen. I denna analys påvisades en fortsatt förhöjd risk för matstrupscancer efter operation jämfört med bakgrundsbefolkningen.

Syftet med **Studie IV** var att undersöka om antirefluxkirurgi kan förhindra uppkomsten av matstrupscancer. Genom ett nordiskt samarbete sammanställdes en databas baserat på nationella register avseende patienter med gastroesofageal refluxsjukdom. Data samlades in från Patientregistret, Cancerregistret, samt Dödsorsaksregistret i de fem nordiska länderna (Danmark, Finland, Island, Norge, och Sverige), samt det svenska Läkemedelsregistret. Studieperioden sträckte sig mellan 1964 och 2014, med variationer mellan länderna baserat på när registren grundades. Risken för cancer jämfördes dels med bakgrundsbefolkningen genom beräkning av stardardiserad incidensratio, justerat för ålder, kön, och kalenderperiod. Vidare jämfördes patienter som genomgått antirefluxkirurgi med ickeopererade patienter (förmodat medicinskt behandlade) genom multivariabel Cox regression justerat för ålder, kön, kalenderperiod, KOL (som ett mått på rökning) samt övervikt. Alla vuxna patienter med gastroesofageal refluxsjukdom inkluderades i studien, och totalt inkluderades 942 906 patienter varav 48 414 genomgått antirefluxkirurgi. Risken för att utveckla matstrupscancer var initialt kraftigt förhöjd både bland patienter som genomgick antirefluxkirurgi och de som inte genomgick operation (medicinskt behandlade), men efter mer än 15 år hade risken minskat och låg därefter på samma nivå som bakgrundbefolkningen. När medicinsk och kirurgisk behandling jämfördes

med varandra sågs liknande minskad risk för att utveckla matstrupscancer vid bägge behandlingarna.

10.3 SLUTSATS

Kirurgisk behandling av halsbränna genom antirefluxkirurgi med titthålsteknik förknippas med mycket låg risk för allvarliga komplikationer och död. Risken för att återfå sin halsbränna efter operation får betraktas som låg, och är särskilt låg hos unga och i övrigt friska män. Effektiv behandling av halsbränna, såväl medicinsk som kirurgisk, minskar risken att utveckla cancer i matstrupen, och efter mer än 15 år ligger risken för matstrupscancer på samma nivå som hos bakgrundsbefolkningen. Dock har användandet av kirurgisk behandling av halsbränna minskat de senaste två decennierna, till förmån för medicinsk behandling.

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