From Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

ANTIREFLUX SURGERY IN THE PREVENTION OF SUPRA-ESOPHAGEAL CANCER AND MORTALITY

Manar Yanes, M.D.

Karolinska Institutet

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-172-5
Cover illustration: by Hsain Al-Shihabi

Antireflux surgery in the prevention of supra-esophageal cancer and mortality
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Manar Yanes

The thesis will be defended in public at Samuelssonsalen, Karolinska Institutet, Solna.
Friday, March 26, 2021, at 10:00

Principal Supervisor:
Professor Jesper Lagergren
Karolinska Institutet
Department of Molecular Medicine and Surgery

Co-supervisors:
Dr. Giola Santoni
Karolinska Institutet
Department of Molecular Medicine and Surgery

Dr. John Maret-Ouda
Karolinska Institutet
Department of Molecular Medicine and Surgery

Associate Professor Eivind Ness-Jensen
Norwegian University of Science and Technology
Department of Public Health and Nursing

Opponent:
Professor Peter Bytzer
University of Copenhagen
Department of Medical and Health Sciences

Examination Board:
Professor Fang Fang
Karolinska Institutet
Department of Environmental Medicine

Professor Magnus Sundbom
Uppsala University
Department of Surgical Sciences

Associate Professor Peter Thelin Schmidt
Karolinska Institutet
Department of Medicine

ABSTRACT

Gastroesophageal reflux disease (GERD), mainly characterized by heartburn or regurgitation, is a common condition in the Western world with an increasing prevalence. GERD is associated with an increased risk of adenocarcinoma of the esophagus, and possibly of supra-esophageal cancers of the larynx, pharynx and lung. GERD is typically treated with antireflux medication, mainly proton pump inhibitors, but an alternative is antireflux surgery with fundoplication. The present thesis aimed to assess outcomes of antireflux surgery with regards to supra-esophageal cancer risk and mortality by conducting multinational population-based cohort studies using the Nordic antireflux surgery cohort (NordASCo), which includes all adult individuals with a documented diagnosis of GERD or antireflux surgery procedure in the national patient registries in any of the five Nordic countries from year 1980 to 2014.

Study I and II investigated whether antireflux surgery decreases the risk of laryngeal and pharyngeal squamous cell carcinoma (Study I) and the risk of small cell carcinoma, squamous cell carcinoma and adenocarcinoma of the lung (Study II) in NordASCo. We calculated standardized incidence ratios (SIR) and hazard ratios (HR) with 95% confidence intervals (CI). The overall risk of laryngeal or pharyngeal squamous cell carcinoma were decreased (SIR 0.62 [95% CI 0.44-0.85] and HR 0.55 [95% CI 0.38-0.80]), and the point estimates decreased further >10 years after surgery. The SIRs and HRs of laryngeal squamous cell carcinoma showed a particular decrease >10 years after surgery (SIR 0.28 [95% CI 0.08-0.72] and HR 0.23 [95% CI 0.08-0.69]). Regarding lung cancer, the overall risk was below unity for small cell (SIR 0.57 [95% CI 0.41-0.77] and HR 0.63 [95% CI 0.44-0.90]) and squamous cell carcinoma (SIR 0.75 [95% CI 0.60-0.92] and HR 0.80 [95% CI 0.62-1.03]), but not for adenocarcinoma (SIR 0.90 [95% CI 0.76-1.06] and HR 1.03 [95% CI 0.84-1.26]).

Study III examined all-cause and disease-specific mortality after antireflux surgery versus antireflux medication in patients with reflux esophagitis or Barrett's esophagus in NordASCo (except for Norway). Compared to antireflux medication, the HRs of mortality from all causes (HR 0.61, 95% CI 0.58-0.63), cardiovascular disease (HR 0.58, 95% CI 0.55-0.61), respiratory disease (HR 0.62, 95% CI 0.57-0.66), laryngeal or pharyngeal cancer (HR 0.35, 95% CI 0.19-0.65), and lung cancer (HR 0.67, 95% CI 0.58-0.80) were decreased, while mortality from esophageal cancer (HR 1.05, 95% CI 0.87-1.28) was not, after antireflux surgery.

Study IV assessed absolute rates and risk factors of poor short-term outcomes following primary laparoscopic and secondary antireflux surgery by using an updated version of NordASCo with the study period 2000-2018. The absolute risk of 90-day mortality and 90-day reoperation was 0.13% and 3.0%, respectively, after primary laparoscopic antireflux surgery, and 0.19% and 6.2%, respectively, after secondary antireflux surgery. Risk estimates of 90-day mortality were increased with higher age and greater comorbidity, and reduced

with higher hospital volume, after primary surgery. Risk estimates of 90-day reoperation were increased with greater comorbidity after primary and secondary surgery. Risk estimates of prolonged hospital stay were increased with higher age and comorbidity after both primary and secondary surgery, and were decreased with higher hospital volume after primary surgery.

In conclusion, antireflux surgery seems to decrease the risk of laryngeal and pharyngeal cancer, as well as small cell carcinoma and squamous cell carcinoma of the lung, and may also decrease the risk of all-cause mortality, and has a favorable safety profile, particularly in younger patients without comorbidity who undergo surgery at high-volume hospitals.

LIST OF SCIENTIFIC PAPERS

I. Yanes M, Santoni G, Maret-Ouda J, Ness-Jensen E, Färkkilä M, Lynge E, Pukkala E, Romundstad P, Tryggvadottir L, von Euler-Chelpin M, Lagergren J.
Laryngeal and pharyngeal squamous cell carcinoma after antireflux surgery in the five Nordic countries.
Annals of Surgery. 2020 Oct 16; Online ahead of print.

II. Yanes M, Santoni G, Maret-Ouda J, Ness-Jensen E, Färkkilä M, Lynge E, Nwaru B, Pukkala E, Romundstad P, Tryggvadottir L, von Euler-Chelpin M, Lagergren J.
Antireflux surgery and risk of lung cancer by histological type in a multinational cohort study
European Journal of Cancer. 2020 Oct; 138:80-88.

III. Yanes M, Santoni G, Maret-Ouda J, Ness-Jensen E, Färkkilä M, Lynge E, Pukkala E, Romundstad P, Tryggvadottir L, von Euler-Chelpin M, Lagergren J.
Survival after antireflux surgery versus medication in patients with reflux oesophagitis or Barrett's oesophagus: a multinational cohort study
British Journal of Surgery. 2021; In press.

IV. Yanes M, Santoni G, Maret-Ouda J, Markar S, Ness-Jensen E, Kauppila J, Färkkilä M, Lynge E, Pukkala E, Tryggvadottir L, von Euler-Chelpin M, Lagergren J.
Mortality, reoperation and hospital stay within 90 days of primary and secondary antireflux surgery in a population-based multinational study
Gastroenterology. 2021 Feb 12; Online ahead of print.

CONTENTS

1 INTRODUCTION

Gastroesofageal reflux disease (GERD), characterized by symptoms of heartburn and regurgitation, affects up to 28% of adults in the world, with a seemingly increasing prevalence in the past two to three decades. While GERD symptoms can affect quality of life and can lead to complications, it is considered a benign disease. Nonetheless, GERD increases the relative risk of esophageal adenocarcinoma, and might also increase the risk of cancer in the larynx, pharynx and lung. GERD is mainly treated with antireflux medication, but antireflux surgery is an alternative option.

The focus of the present thesis is on antireflux surgery in relation to supra-esophageal cancer development, long-term survival, and short-term postoperative outcomes.

This thesis includes four original studies based on a cohort of adult individuals with GERD from any of the five Nordic countries from year 1980 onwards. The first study investigates the influence of antireflux surgery on laryngeal and pharyngeal cancer. The second study evaluates antireflux surgery and risk of lung cancer. The third study examines long-term survival after antireflux surgery compared to antireflux medication. The fourth study assesses the risk of poor short-term postoperative outcomes after antireflux surgery.

2 BACKGROUND

2.1 GASTROESOPHAGEAL REFLUX DISEASE

The anatomy of the gastroesophageal junction is essential to understanding the pathophysiology and treatment options of gastroesophageal reflux disease (GERD). This junction connects the esophagus to the stomach and is located where the proximal longitudinal folds of the stomach begin. This location is normally also where the diaphragmatic compression is seen as well as where the esophageal squamous epithelium changes to columnar epithelium, also called the squamocolumnar junction, or Z-line (Figure 1).(1) In order to maintain an antireflux barrier at this site, the lower esophageal sphincter contains intrinsic smooth muscles encircled by the crural diaphragm, and supported by the stomach's sling fibers (creating the angle of His) located underneath the sphincter.(1) This enables a dynamic exertion of pressure depending on the varying local physiologic conditions. The most common mechanisms underlying GERD are prolonged transient relaxations of the lower esophageal sphincter and hiatal herniation.(2) Transient relaxations of the lower esophageal sphincter, including the crural diaphragm, is a physiologic event mediated by a vagal reflex that is independent of swallowing, and allows venting of gas from the stomach.(1, 2) In patients with GERD, it is believed that an increased compliance of the gastroesophageal junction and an elevated pressure gradient over the junction facilitate reflux of stomach content to the esophagus during these relaxations.(3) Hiatal herniation anatomically disrupts the antireflux barrier by dislocating the proximal stomach partly reaching into the thoracic cavity, which can impair the flap valve mechanism created by the stomach's sling fibers, counteract the clearance of acid from the esophagus, and impair the pinchcock-like action exerted on the lower esophageal sphincter by the crural diaphragm.(1, 2)

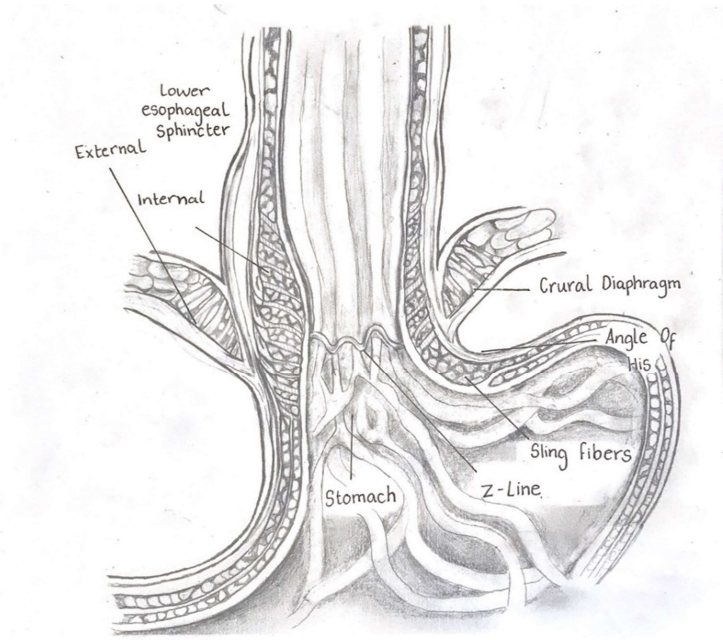

Illustration by Noor Kerdi.

Figure 1. *Anatomy of the gastro-esophageal junction.*

Since the mid-1990s, the overall prevalence of GERD seems to have increased,(4, 5) and GERD is currently a common condition that affects 9% to 28% of adults in the Western world and the Middle East, and 3% to 8% of adults in East Asia.(5) Prevalence of GERD

increases with higher age in adults, and women seem to have slightly higher prevalence of GERD than men.(6) The main risk factors for developing GERD are heredity, obesity, and tobacco smoking.(3, 4, 7, 8) In twin studies, a heritability of 31%-43% has been found.(9, 10) Obesity is dose-dependently associated with GERD, particularly central obesity, while tobacco smoking has a weaker but consistent association with GERD.(3, 6, 7, 11) In a recent meta-analysis including 22 studies investigating association between obesity and GERD, and 30 studies investigating association between tobacco smoking and GERD, the odds ratio (OR) of GERD in individuals with obesity compared to no obesity was 1.73 (95% CI, 1.46-2.06), and in smokers compared to non-smokers the OR was 1.26 (95% CI, 1.04-1.52).(6) Lifestyle changes that can reduce symptoms of GERD are mainly weight loss and smoking cessation.(12) High alcohol consumption and dietary factors can precipitate reflux episodes among patients with GERD, but these exposures have not been found to be associated with the development of GERD.(3)

GERD is defined as a "condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications", according to the Montreal global evidence-based consensus.(13) The characteristic symptoms of GERD are heartburn and regurgitation of acidic gastric content, i.e. sensation of retrosternal burning and sensation of sourness in the pharyngeal or oral cavity.(3, 13) These symptoms vary in frequency and intensity, and are often regarded as troublesome and affecting health-related quality of life when mild symptoms are experienced two or more days per week, or severe symptoms are experienced more than one day per week.(3, 13) In most patients, the severity of GERD will not increase with time.(13, 14) Complications of GERD include reflux esophagitis, strictures, dysphagia, columnar cell metaplasia (Barrett's esophagus), and esophageal adenocarcinoma, and the presence of these complications (except for esophageal adenocarcinoma) is together with the typical symptoms part of the definition of GERD.(3, 13)

GERD is mainly a clinical diagnosis, mostly based on the cardinal symptoms of heartburn or regurgitation, and alleviation of symptoms following a course of proton pump inhibitor (PPI) treatment.(13, 15) Upper gastrointestinal endoscopy and pH monitoring have low sensitivity in assessing presence of GERD, compared to assessment of the cardinal symptoms of GERD, but the latter has a limited specificity.(13, 15) Nonetheless, upper gastrointestinal endoscopy should be considered if symptom control is not achieved by a standard course of PPI and if malignancy warning symptoms are present, i.e. involuntary weight loss, worsening of dysphagia, or signs of gastrointestinal bleeding. If no GERD-related complications are present at endoscopy, a 24-hour pH monitoring can be performed to assess abnormal acid exposure.(3, 13, 15)

2.2 TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

2.2.1 Antireflux medication

2.2.1.1 Proton pump inhibitors

PPIs are the most commonly used and most effective antireflux medication therapy of GERD.(16, 17) PPIs act on the gastric parietal cells by irreversibly blocking the H^+/K^+ ATPase, which inhibits acid production in the parietal cells of the stomach.(18) Although there are several different PPI drugs, no major difference in reflux symptom control has been observed among them.(19) PPI therapy relieves symptoms of heartburn in 37% to 61% of patients with GERD who do not have esophagitis. In patients with esophagitis, 56% to 77% experience relief of heartburn, and in 72% to 83% of the cases PPI leads to esophagitis healing.(16, 17, 20-22) In contrast, PPI use reduces symptoms of regurgitation by 26% to 64%, which is only 17% more than what is achieved with placebo in patients with GERD.(23, 24) An explanation is that PPI does not prevent duodeno-gastric reflux, but only reduces its acidic component.(25) Thus, regurgitation will typically remain although with less acidic contents. Current guidelines in the treatment of GERD recommend initiation of an 8-week course of PPI therapy, once a day. This dose can be increased to twice daily if the relief of symptoms is insufficient.(26) In patients who relapse in GERD after discontinuing PPI therapy, long-term or sometimes life-long use of lowest possible dose of PPI might be required.(26, 27) Concerns have arisen regarding side-effects of long-term use of PPI. Although the evidence is inconsistent, an increased risk of osteoporosis, bone fractures, Clostridium difficile-associated diarrhea, and gastrointestinal malignancies (mainly gastric cancer) following long-term therapy with PPIs has been suggested.(27)

2.2.1.2 Histamine-2 receptor antagonists

Histamine-2 receptor antagonists is a class of anti-acid medication that pre-dates PPIs, and reduces gastric acidity by acting as a reversible antagonist of histamine-2 receptors in the stomach's parietal cells.(28) This anti-acid is better than placebo, but less effective in relieving symptoms of heartburn and healing esophagitis than PPI.(17, 22) Histamine-2 receptor antagonists are presently mostly used in conjunction with PPI to enhance symptom relief or as a step-down therapy from PPI use.(26)

2.3 ANTIREFLUX SURGERY

The general concept of antireflux surgery (also called fundoplication) is to revive the capacity of the antireflux barrier at the site of the gastroesophageal junction by removing any herniation, restoring the angle of His and mechanically stabilizing the lower esophageal sphincter.(29) In order to accomplish this, the distal esophagus is mobilized to an appropriate intra-abdominal length (about 3 cm), and the fundus of the stomach is mobilized and wrapped around the distal esophagus.(29, 30) In the presence of hiatal hernia, an approximation (tightening) of the crural diaphragm is also performed.(29, 30) Thus, fundoplication mechanically and physiologically strives to achieve control of acidic and non-acidic duodeno-gastric reflux, including enzymes, bile-salts and pancreatic juice.(31) Rudolph Nissen first described the technical elements of antireflux surgery in 1956, which included wrapping of the fundus by 360 degrees around the esophagus. Several modified techniques have been devised by other surgeons following studies that has shown an increased risk of dysphagia and bloating with the Nissen technique, the two most common becoming partial posterior wrapping of the fundus by 180 to 270 degrees (according to Toupet), or partial anterior wrapping of the fundus by 180 degrees (according to Dor) (Figure 2).(29) In the early 1990s, laparoscopic antireflux surgery was introduced, which yielded similar reflux symptom control compared to open surgery, but reduced postoperative morbidity, length of hospital stay and sick leave, and improved cosmetics, thus making it the procedure of choice in antireflux surgery treatment.(32, 33) The introduction of laparoscopic antireflux surgery led to a surge in antireflux surgery procedures in the 1990s in the Western world, including the Nordic countries, which has declined over time following increased use of PPI since the early 2000s (Figure 3).(34, 35)

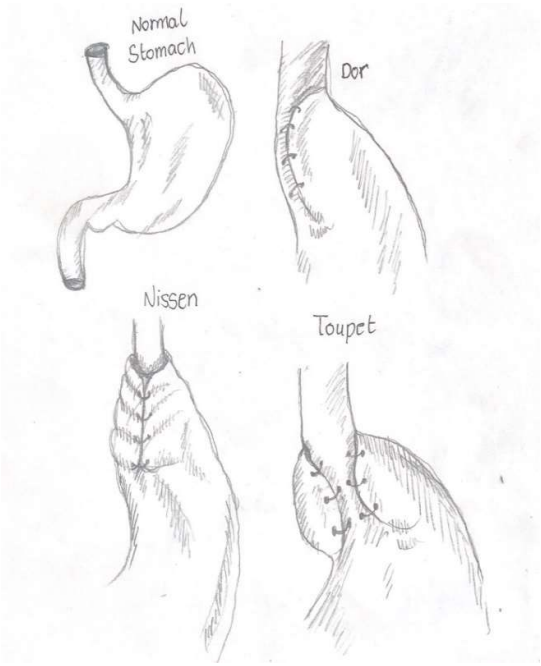

Illustration by Noor Kerdi.

Figure 2. *Antireflux surgery techniques named after the surgeons that introduced them.*

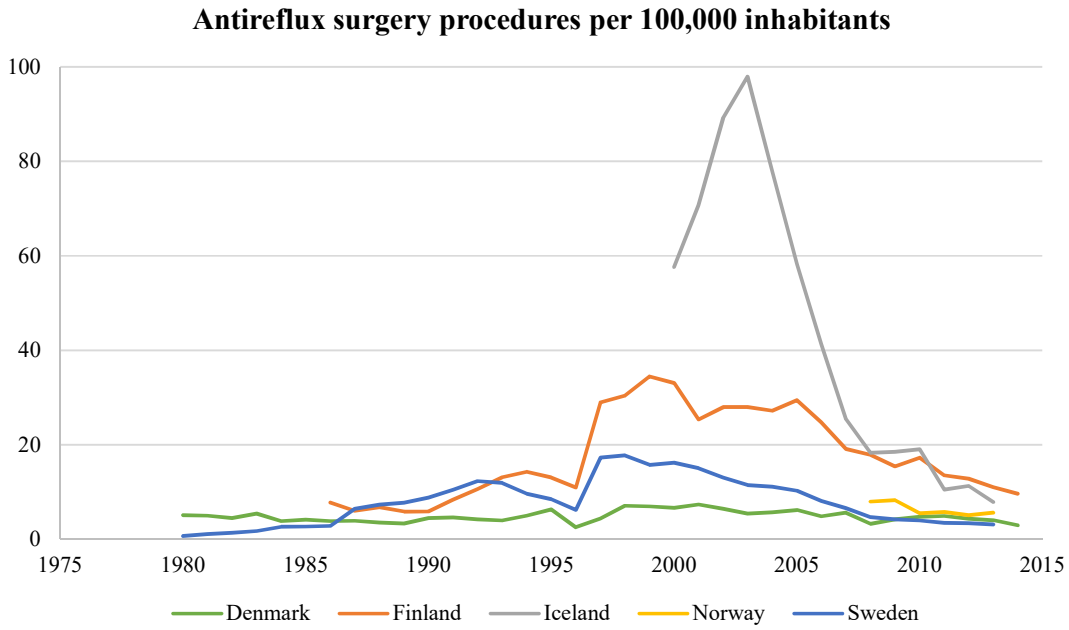

Figure 3. *Number of antireflux surgery procedures per 100,000 inhabitants in the five Nordic countries from 1980 to 2014 based on data from the Nordic Antireflux Surgery Cohort.*

Several prospective randomized clinical trials and meta-analyses have found similar reflux control after total posterior antireflux surgery technique and partial posterior or partial anterior antireflux surgery techniques.(36-42) However, two meta-analyses showed that anterior techniques might be inferior to posterior techniques concerning reflux control.(43, 44) Further, three meta-analyses observed that partial antireflux surgery techniques result in less postoperative dysphagia and gas-related symptoms compared to a total wrap.(36-38) This is supported by a recent randomized clinical trial of 456 participants, which showed a mean dysphagia score of 1.3 (SD, 0.9) at 2 years after antireflux surgery with 270 degree posterior wrap compared to 1.7 (SD, 1.2) with a 360 degree total wrap.(42)

Antireflux surgery is considered to be a long-lasting treatment for GERD, and studies have shown reflux symptom control in 80-90% of patients at up to 10 years after surgery.(45-47) Nonetheless, medical intervention and surgical reintervention with secondary antireflux surgery (reoperation) can be required, mainly because of recurrence of GERD. A Swedish study of 2655 patients who had undergone primary antireflux surgery showed a reoperation rate of 2.9% within a median follow-up of 5.6 years, a study including 13,050 patients from the United States observed a reoperation rate of 6.8% within 10 years after primary antireflux surgery, and a recent Danish study of 3,717 participants found a reoperation rate of 12.8% after 15 years of primary antireflux surgery.(34, 47, 48)

Severe postoperative complications after antireflux surgery are uncommon. In Western populations, short-term postoperative mortality rates are reported to be up to 0.6% after primary antireflux surgery and up to 0.8% after secondary antireflux surgery. Rates of other severe postoperative complications that are not lethal occur in up to 4.8% of cases.(35, 49-53)

Compared to medical treatment, antireflux surgery seems to have similar or slightly superior reflux symptom control in the treatment of GERD. Some studies have also shown a slightly superior overall and GERD-associated quality of life, and long-term cost-effectiveness of antireflux surgery compared to medication.(26, 54-56) In a study from the United States that included 1,892 GERD patients, the cumulative all-cause mortality rate was 47% in participants using antireflux medication and 37% in those who had undergone antireflux surgery.(57) In contrast, another study from the United States including 239 patients with GERD found increased all-cause mortality (relative risk 1.57, 95% confidence interval [CI] 1.01-2.46) after antireflux surgery, compared to antireflux medication.(58) Because antireflux surgery carries a risk of complications, which are rare but still present and sometimes severe, medical therapy is recommended as first-line treatment of GERD.(35, 56) Thus, antireflux surgery is mainly considered in fit patients with an objectively confirmed diagnosis of GERD that respond well to PPI but do not tolerate or wish long-term PPI-treatment.(8)

2.4 EXTRAESOPHAGEAL MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX DISEASE

Except for the more common symptoms affecting the esophagus, patients with GERD can also present with extraesophageal manifestations in the larynx, pharynx, and lungs.(59, 60) While GERD seldom is the sole cause of extraesophageal manifestations, a significant association has been established with chronic cough, laryngitis, and asthma.(13, 60, 61) These manifestations are believed to be due to duodeno-gastric contents reaching above the esophagus, leading to laryngo-pharyngeal reflux and airway micro-aspiration, or due to a esophageal-bronchial reflex mediated by the vagal nerves.(60, 62) The laryngeal and pharyngeal epithelium seems to be particularly vulnerable to inflammatory damage following contact with acidic and non-acidic duodeno-gastric contents, including hydrochloric acid, pepsin, and bile-salts.(63-67) Suggested associations with other laryngo-pharyngeal and lung diseases include pharyngitis, globus pharyngeus, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and bronchiolitis obliterans syndrome.(60, 61, 68, 69)

The evidence of the efficacy of PPI therapy is scant in extraesophageal manifestations of GERD. In patients with laryngeal symptoms and chronic cough, less than 25% respond to PPI therapy,(70, 71) and in patients with asthma and concomitant heartburn, reflux esophagitis or Barrett's esophagus, PPI therapy can improve peak expiratory flow but with limited clinical relevance.(72) Airway symptoms due to GERD may arise regardless of reflux acidity,(73) which might explain the limited efficacy of PPI therapy. Thus, clinical guidelines recommend objectively ensuring presence of GERD before initiating a PPI course for these indications.(26)

Antireflux surgery is sparsely studied with regards to extraesophageal manifestations of GERD. A subset of patients with extraesophageal symptoms, concomitant cardinal symptoms of GERD, and previous response to antireflux medication seem to respond better to antireflux surgery compared to patients primarily presenting with extraesophageal symptoms.(74, 75) A recent systematic review found that, following antireflux surgery, 83% of patients with

laryngopharyngeal reflux experienced partial symptom relief and 67% regarded themselves cured.(76) There is evidence that in patients with GERD, antireflux surgery might reduce chronic cough and asthma symptoms,(77-81) and improve pulmonary function and counteract rejection in lung transplantation patients.(82-84) Nonetheless, since the current evidence is sparse, and antireflux surgery might provide resolution of extraesophageal symptoms only in selected cases, the clinical guidelines generally do not recommend antireflux surgery in patients who do not have objectively verified reflux as the cause of extraesophageal symptoms, or do not respond to PPI therapy.(26, 85)

2.5 GASTROESOPHAGEAL REFLUX DISEASE AND ANTIREFLUX TREATMENT IN RELATION TO RISK OF SUPRA-ESOPHAGEAL CANCER

GERD is an established and dose-dependent risk factor of esophageal adenocarcinoma,(86) and yet, antireflux surgery does not seem to prevent this tumor.(87) Esophageal adenocarcinoma is beyond the scope of the present thesis. GERD appears also to be associated with cancer of the larynx and pharynx,(88-98) and an association with lung cancer has been suggested.(99-103) A few recently published studies have provided some relevant findings in this respect. A population-based case-control study from the United States found that the risk was nearly two times higher in developing laryngo-pharyngeal squamous cell carcinoma among individuals with GERD who were neither heavy smokers nor heavy alcohol drinkers (OR 1.78, 95% CI 1.00-3.16).(92) In a meta-analysis, the risk of developing laryngeal cancer was more than two times higher among individuals with GERD or laryngo-pharyngeal reflux, after controlling for tobacco smoking and alcohol intake (OR 2.07, 95% CI 1.26-3.41).(93) These findings were recently supported by a matched case-control study of 2,094 participants from the United States, showing that after adjusting for tobacco smoking and alcohol intake, the risk of laryngeal cancer was increased (OR 1.29, 95% CI 1.04-1.59) in participants with GERD.(98) In addition, a very recent meta-analysis showed an increased risk for laryngeal cancer (OR 1.95, 95% CI 1.33–2.86), and suggested an increased risk also of pharyngeal cancer (OR 1.56, 95% CI 0.86–2.83) in patients with GERD.(104) Finally, a recent population-based cohort study observed that individuals with GERD had a more than 50% increased risk of lung cancer after controlling for tobacco smoking (hazard ratio 1.53, 95% CI 1.19-1.98).(103) Antireflux surgery has not been studied in relation to the risk of any of these supra-esophageal cancers. Only one study has investigated antireflux medication (PPI and histamine-2 receptor antagonist) in relation to the risk of developing laryngo-pharyngeal squamous cell carcinoma, showing a 41% decrease after treatment (OR 0.59, 95% CI 0.38-0.93).(92)

2.5.1 Cancer of the larynx

The larynx is an upper airway organ that is mainly composed of a cartilaginous skeleton and is located anterior to the hypopharynx, at cervical vertebrae level of C3 to C7.(105) The larynx is composed of three subsites, i.e. supraglottis, glottis, and subglottis (Figure 4). Main functions of larynx are protection of trachea and the lungs from aspiration and phonation through the vocal cords.(105) Laryngeal cancer is one of the most common tumors of the respiratory tract, affecting men around five times more often than women.(105) The main histological type of laryngeal cancer is squamous cell carcinoma, which approximately account for 90% of all laryngeal malignancies.(106) Common warning symptoms of laryngeal cancer include hoarseness, dysphonia, and dysphagia, which should prompt clinical examination and further investigation with flexible nasopharyngoscopy for inspection or direct laryngoscopy with biopsies.(105) At diagnosis, about 60% of patients have reached an advanced tumor stage (III or IV).(105) Depending on location, tumor stage, and local traditions at specialized medical centers, treatment might include radiotherapy with or without surgery, or surgery alone.(105, 107) The overall 5-year survival is 63%.(105) The main risk factors are tobacco smoking and heavy alcohol consumption, and these exposures seem to increase the risk of laryngeal cancer by 10 times and 2.5 times, respectively.(108) Except for the possible association between GERD and laryngeal cancer, additional potential risk factors are occupational exposures, textile dust, and red meat.(109, 110)

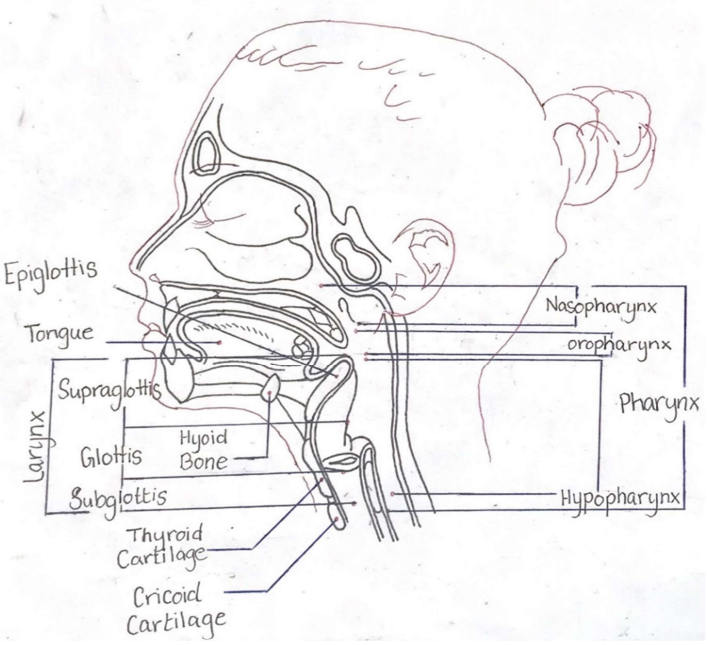

Illustration by Noor Kerdi.

Figure 4. *Anatomy of larynx and pharynx.*

2.5.2 Cancer of the pharynx

Pharyngeal cancer is predominantly squamous cell carcinoma and is mainly categorized based on the subsite from where it arises, i.e. nasopharynx, oropharynx, or hypopharynx (Figure 4).(111) Globally, the incidence rate of pharyngeal cancer ranges from 0.8 to 1.4 cases per 100,000 person-years depending on the subsite,(111) and this tumor occurs two to three times more frequently in men than in women.(112-115) Depending on tumor site, warning symptoms include dysphagia, odynophagia, dysarthria, epistaxis, unilateral nasal obstruction, and neck mass.(116) Diagnosis and treatment of pharyngeal cancer include a similar approach to that of laryngeal cancer, but treatment might also include systemic

chemotherapy in selected cases.(116) Among the three subsites, the overall 5-year survival rate is lowest in hypopharyngeal cancer, ranging from 25 to 40%.(113) The main risk factors of pharyngeal cancer are tobacco smoking and heavy alcohol consumption.(117, 118) Except for suggested association with GERD, oropharyngeal cancer and nasopharyngeal cancer are specifically associated with human papilloma virus and Epstein-Barr virus infection, respectively.(112, 115)

2.5.3 Cancer of the lung

Lung cancer is estimated to cause 1.6 million deaths per year, making it the most common cause of cancer-related death globally.(119) The major histological types of lung cancer are adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma (SCLC). Together with other less common histological types of lung cancer, adenocarcinoma and squamous cell carcinoma are collectively classified as non-small cell lung carcinoma (NSCLC).(120) NSCLC constitute about 85% of all lung cancer, with the rest of cases being SCLC, which is a type of neuroendocrine tumor.(120, 121) Although histologically different, NSCLC and SCLC can arise in a combined form in lung cancer patients, and there is growing evidence that these lung tumors share origins in multipotent stem cells.(121) Unfortunately, most lung cancer patients are diagnosed at an advanced tumor stage because of late presentation of clinical symptoms and the absence of effective screening programs**.**(122) NSCLC has an overall 5-year survival of 25%, and a 5-year survival of 5.5% in patients with distant metastases.(123) SCLC is even more aggressive with rapid growth, early development of metastases, and an overall 5-year survival of only 6%.(124) The main risk factor of both NSCLC and SCLC is tobacco smoking, accounting for around 80% of lung cancer cases in men and 50% of lung cancer cases in women, globally.(125) Other established risk factors are genetic susceptibility, air pollution, radon exposure, occupational exposures (mainly asbestos), and high doses of radiation.(122, 125) Further, asthma, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis seem to increase the risk of developing lung cancer beyond the effects of their shared risk factor tobacco smoking.(126-128) Over the past two decades, progress has been made in improving clinical outcomes of patients with NSCLC.(120) However, only modest improvement of detection, therapy, and survival has been achieved in patients with SCLC over the past three decades.(129) The most effective preventive measure in all major histological types of lung cancer is smoking cessation, which substantially reduces the risk of dying from this cancer.(121, 122)

3 AIMS

The overall aim of the present thesis is to assess antireflux surgery in the prevention of supra-esophageal cancer risk and mortality.

The study-specific aims are:

- To clarify whether antireflux surgery for GERD prevents laryngeal or pharyngeal squamous cell carcinoma (Study I)
- To assess the risk of lung cancer by histological type in patients with GERD following antireflux surgery (Study II)
- To investigate all-cause mortality and disease-specific causes of mortality after antireflux surgery for GERD (Study III)
- To assess the absolute risks and risk factors for poor short-term outcomes after primary laparoscopic and secondary antireflux surgery for GERD (Study IV)

4 METHODS

4.1 OVERVIEW

Table 1. *Overview of methods used in the studies of the thesis.*

	Study I	**Study II**	**Study III**	**Study IV**
Design	Population-based cohort study	Population-based cohort study	Population-based cohort study	Population-based cohort study
Data sources	Nordic national registries: Patient Registries, Cancer Registries, Cause of Death Registries	Nordic national registries: Patient Registries, Cancer Registries, Cause of Death Registries	Nordic national registries: Patient Registries, Cancer Registries, Cause of Death Registries and Swedish Prescribed Drug Registry	Nordic national registries: Patient Registries, Cancer Registries, Cause of Death Registries
Period	1980-2014	1980-2014	1980-2014	2000-2018
Inclusion	GERD diagnosis in the national patient registry	GERD diagnosis in the national patient registry	GERD diagnosis in the national patient registry	Antireflux surgery procedure in the national patient registry
Exposure	Antireflux surgery	Antireflux surgery	Antireflux surgery and antireflux medication	Age, sex, comorbidity, hospital volume, and calendar period
Main outcome(s)	Laryngeal or pharyngeal squamous cell carcinoma	Small cell, squamous cell carcinoma, and adenocarcinoma of the lung	All-cause mortality and disease-specific mortality	Mortality within 90 days, reoperation within 90 days and prolonged hospital stay
Measures of effect	Standardized incidence ratio and multivariable Cox regression	Standardized incidence ratio and multivariable Cox regression	Cox regression	Multivariable logistic regression
Covariates	Sex, age, calendar period, country, obesity, chronic obstructive pulmonary disease and excessive alcohol intake	Sex, age, calendar period, country, obesity and chronic obstructive pulmonary disease	Sex, age, calendar period, country and comorbidity	Sex, age, comorbidity, calendar period and country

4.2 DATA SOURCES

4.2.1 The patient registries in the Nordic countries

The patient registries in the Nordic countries include data on patient characteristics, dates of admission and discharge, and diagnosis and surgical procedure codes, all from in-hospital and specialized out-patient care. The diagnosis codes registered in each national patient registry follow the International Statistical Classification of Diseases and Related Health Problems (ICD), with some country-specific variations in the coding. In Finland and Sweden, the ICD-versions used in the national patient registries have been updated rather simultaneously following each update of the ICD. In Denmark, the national patient registry migrated directly from ICD version 8 to version 10, while in Iceland and Norway, ICD version 10 has been used since the inception of their respective national patient registry.(130) The Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures was introduced in 1996, and was adopted by all Nordic countries closely thereafter, which provided a more standardized approach to surgical procedure coding and enabled distinction between open and laparoscopic procedures.(131) Nationwide coverage of in-hospital care in the patient registries was reached in the 1970s (Finland), 1978 (Denmark), 1987 (Sweden), 1997 (Norway), and 1999 (Iceland). While the patient registry of Iceland does not include specialized out-patient care, coverage of specialized out-patient care in the other Nordic countries has been nationwide from 1994 (Finland), 1995 (Denmark), 2001 (Sweden), and 2006 (Norway). The completeness of the national patient registries is high because the healthcare in the Nordic countries is mainly public, the reporting to the national patient registries is mandatory by law, and the reimbursement to the healthcare providers depend on this reporting.(132, 133) The validity of the national patient registries has been mainly investigated in Denmark, Finland, and Sweden, and studies have shown a positive predictive value of 15-100%, 75-99%, and 85-95%, respectively.(130, 134, 135)

4.2.2 The cancer registries in the Nordic countries

The national cancer registries in the Nordic countries include data on date of cancer diagnosis, patient demographics at cancer diagnosis, histological type and location of the tumor, and source of cancer confirmation. All Nordic cancer registries have very high national completeness from their initiation in 1943 (Denmark), 1953 (Finland), 1953 (Norway), 1955 (Iceland) and 1958 (Sweden).(136) The reporting to the registries has been mandatory from or shortly after their inception, except for in Denmark, where reporting became mandatory in 1987.(133) Microscopic verification of the registered tumors ranges between 93-98% between the Nordic countries. Numerous validation studies have shown high completeness (≥98%) and accuracy (≥94%) of the cancer registration.(136)

4.2.3 The cause of death registries in the Nordic countries

The national cause of death registries contain information on date of death, and primary and other underlying causes of death, mainly collected from death certificates. These national registries have been nationwide with mandatory registration since their initiation in 1951

(Norway), 1952 (Sweden), 1952 (Iceland), 1969 (Finland) and 1970 (Denmark).(133) The completeness of date of death and cause of death in the Swedish cause of death registry has been shown to be 100% and 96% complete, respectively.(137) A Swedish study has shown 77% agreement between cause of death according to the medical records, compared to cause of death in the Swedish cause of death registry.(138)

4.2.4 The registries of the total population in the Nordic countries

The national registries of the total population include data such as birth and country of birth, sex, death, marital status, migration and citizenship. These registries have been nationwide since 1953 (Iceland), 1964 (Norway), 1968 (Denmark), 1968 (Sweden), and 1971 (Finland), and are considered entirely representative of the total national populations with virtually no loss to follow-up. The reporting of births and deaths within 30 days to these registries is estimated to be 100%.(139, 140)

4.2.5 The prescribed drug registry in Sweden

The Swedish prescribed drug registry include data on all prescribed and dispensed medications in Sweden, and has been nationwide since initiation in July 1, 2005. The coverage is virtually 100% and the reporting is mandatory according to Swedish law.(141)

4.2.6 Nordic antireflux surgery cohort

This thesis utilizes the Nordic antireflux surgery cohort (NordASCo) as the source cohort. This cohort has been presented in detail in a separate cohort profile.(133) In short, NordASCo is a population-based cohort that includes merged data from the national patient registries, cancer registries and cause of death registries in the five Nordic countries, i.e. Denmark, Finland, Iceland, Norway, and Sweden. The inclusion criteria in NordASCo is a documented GERD diagnosis or antireflux surgery procedure recorded in a national patient registry in any Nordic country from year 1980 to 2014 (Supplementary Table 1). There are differences in the start and end years between the countries, which is due to availability of data. The start and end years were 1980-2014 (Denmark), 1980-2013 (Sweden), 1986-2013 (Finland), 2000-2013 (Iceland), and 2008-2013 (Norway). More recently, NordASCo was updated to also include data from 1980-2018 in Finland and 1980-2018 in Sweden. The similar structure of the national health data registries in the Nordic countries, combined with the well-established system of a unique personal identity number assigned to each resident in all Nordic countries, allowed linkages of the individuals' data between the registries and merging of the collected data.(133, 142)

4.3 STUDY DESIGN

4.3.1 Study I

4.3.1.1 Design

Population-based cohort study in the five Nordic countries that investigated the risk of laryngeal and pharyngeal squamous cell carcinoma after antireflux surgery or no such surgery in patients with GERD, from 1980 through 2014.

4.3.1.2 Cohort

This study was based on NordASCo and included a main cohort and a sub-cohort. The main cohort included participants with a documented diagnosis of GERD in any of the national patient registries in the Nordic countries and were aged ≥18 and ≤95 years at the time of first GERD diagnosis. The sub-cohort was restricted to participants with severe GERD diagnosis that require objective confirmation by endoscopy and histology, i.e. reflux esophagitis or Barrett's esophagus. Excluded were patients with recorded laryngeal or pharyngeal carcinoma before diagnosis of GERD. Moreover, participants from Norway were excluded from the sub-cohort because the four-character sub-categories of diagnosis codes that are required for identification of severe GERD were not available in the Norwegian patient registry. The outcomes laryngeal and pharyngeal squamous cell carcinoma were identified through the national cancer registries of each country.

4.3.1.3 Follow-up

To counteract detection bias of earlier detection of laryngeal or pharyngeal squamous cell carcinoma due to the diagnosis of GERD or the antireflux surgery procedure, the first year of follow-up was excluded. A participant contributed to person-years at risk to the antireflux surgery group with GERD from one year after the date of antireflux surgery procedure, until the date of laryngeal or pharyngeal squamous cell carcinoma, death, or end of study period, whichever occurred first. A participant contributed to person-years at risk to the non-operated group with GERD from one year after the date of first GERD diagnosis, until the date of laryngeal or pharyngeal squamous cell carcinoma, antireflux surgery, death, or end of study period, whichever occurred first.

4.3.1.4 Statistical analysis

Measures of effect were calculated by using two statistical methods. In the first approach, the incidence of laryngeal and pharyngeal squamous cell carcinoma in the antireflux surgery group and the non-operated group was compared to their corresponding general Nordic background population. Standardized incidence ratios (SIR) and 95% CIs were calculated by dividing the observed number of laryngeal or pharyngeal squamous cell carcinoma in the cohort groups by the expected number among individuals of the same country, sex (men or women), age (5-year categories), and calendar period (5-year categories). The SIRs were calculated for the overall follow-up period, and stratified into the follow-up categories >1-5,

>5-10, >10-15, and >15 years. In the second approach, the incidence of laryngeal and pharyngeal squamous cell carcinoma in the antireflux surgery group was compared directly to the non-operated group by using multivariable Cox regression to calculate hazard ratios (HR) and 95% CIs, adjusted for sex (male or female), age (continuous), calendar period (1980-1989, 1990-1999, or 2000-2014), country (Denmark, Finland, Iceland, Norway, or Sweden), chronic obstructive pulmonary disease (yes or no), obesity diagnosis or diabetes mellitus type 2 (yes or no), and alcohol-related diagnoses (yes or no). The HRs were calculated for the entire follow-up period and for the same follow-up categories as above.

4.3.2 Study II

4.3.2.1 Design

Population-based cohort study in the five Nordic countries that investigated the separate risk of small cell carcinoma, squamous cell carcinoma, and adenocarcinoma of the lung following antireflux surgery or no such surgery for GERD in 1980 to 2014.

4.3.2.2 Cohort

Similar to Study I, this study cohort used NordASCo and had a main cohort of participants with any GERD and a sub-cohort of participants with severe GERD, i.e. reflux esophagitis or Barrett's esophagus. Participants were aged ≥18 and ≤95 years at the time of first GERD diagnosis. Participants with any recorded lung cancer before diagnosis of GERD were excluded, and Norwegian GERD patients were excluded from the sub-cohort due to unavailability of four-character sub-categories in the Norwegian patient registry, which are required for identification of esophagitis and Barrett's esophagus. The outcomes small cell carcinoma, squamous cell carcinoma, and adenocarcinoma of the lung were identified through the national cancer registries of each country. Individuals who were identified with histological subtypes that were ill-defined, or that potentially represented poor or undifferentiated forms of lung cancer, were excluded to avoid misclassification.

4.3.2.3 Follow-up

The follow-up was the same as in Study I. Accumulation of person-years at risk to the antireflux surgery group started from one year after the date of antireflux surgery, until the date of any lung cancer, death, or end of study period. Accumulation of person-years at risk to the non-operated group started from one year after the date of first GERD diagnosis, until the date of any lung cancer, antireflux surgery, death, or end of study period.

4.3.2.4 Statistical analysis

The two statistical approaches to calculating measures of effect in Study I were similarly applied in Study II. The incidence of small cell carcinoma, squamous cell carcinoma, and adenocarcinoma of the lung in the antireflux surgery group and the non-operated group was compared to the background population by calculating SIRs and 95% CIs. This was performed by dividing the observed cases of small cell carcinoma, squamous cell carcinoma,

and adenocarcinoma of the lung in the antireflux surgery group and the non-operated group by the expected cases in individuals of the corresponding country, sex (men or women), age (5-year categories), and calendar period (5-year categories). SIRs were computed for the entire follow-up period, and categorized into >1-5, >5-10, >10-15, and >15 years of follow-up. Secondly, calculation of incidence rate ratio of small cell carcinoma, squamous cell carcinoma, and adenocarcinoma of the lung was performed, comparing tumor incidence in the antireflux surgery group to that of the non-operated group. For this purpose, a multivariable Cox regression was applied, which provided HRs and 95% CIs, adjusted for sex (male or female), age (continuous), calendar period (1980-1989, 1990-1999, or 2000-2014), country (Denmark, Finland, Iceland, Norway, or Sweden), chronic obstructive pulmonary disease (yes or no), and obesity diagnosis or diabetes mellitus type 2 (yes or no). The HRs were computed for overall follow-up, and categorized as in the SIR-analyses.

4.3.3 Study III

4.3.3.1 Design

Multinational population-based cohort study that investigated mortality, comparing patients with reflux esophagitis or Barrett's esophagus who have undergone antireflux surgery with those using antireflux medication from 1980 to 2014.

4.3.3.2 Cohort

This cohort included all individuals aged ≥18 and ≤70 years with a documented diagnosis of objectively determined reflux esophagitis or Barrett's esophagus in NordASCo, except for Norway where data on reflux esophagitis or Barrett's esophagus were not available. Individuals with documented cancer in the esophagus, larynx, pharynx or lung before diagnosis of reflux esophagitis or Barrett's esophagus were excluded. The outcomes were all-cause mortality (main), and disease-specific mortality (secondary), i.e. mortality from cardiovascular disease, respiratory disease, esophageal cancer, laryngeal or pharyngeal cancer, or lung cancer. These were identified in the cause of death registries.

4.3.3.3 Exposure

Individuals with reflux esophagitis or Barrett's esophagus who had documented open or laparoscopic antireflux surgery in the national patient registries were compared with those using antireflux medication (mainly proton pump inhibitors, or occasionally histamine-2 receptor antagonists). Direct data on antireflux medication were available from the Swedish prescribed drug registry, which was utilized to confirm the use of antireflux medication in a validation sample of 7,339 Swedish non-operated participants with reflux esophagitis or Barrett's esophagus. Among these, 7,143 (97.3%) had dispensed prescriptions of antireflux medication, of whom 6,530 (91.4%) obtained their first prescription within 3 months before or after their diagnosis date.

4.3.3.4 Follow-up

Follow-up of study participants began from the first diagnosis date of reflux esophagitis or Barrett's esophagus, until date of antireflux surgery, death or end of study. Participants who underwent antireflux surgery were censored from the non-operated group at the date of antireflux surgery, and were from that date included in the follow-up of the antireflux surgery group instead.

4.3.3.5 Statistical analysis

Multivariable Cox regression was used to calculate HRs and 95% CIs, comparing mortality in the antireflux surgery group to that of the antireflux medication group. Five potential confounders were adjusted for in the model: sex (female or male), age (continuous variable), calendar period (1980-1989, 1990-1999, or 2000-2014), country of residence (Denmark, Finland, Iceland, or Sweden), and comorbidity (Charlson Comorbidity Index score 0, 1, or ≥2). HRs were calculated for the entire follow-up period, and for four follow-up categories: 0-5, >5-10, >10-15, and >15 years. Stratification by sex, age, comorbidity, and surgical approach (open or laparoscopic fundoplication) was performed in the analyses of all-cause mortality (main outcome). Analyses including surgical approach were restricted to a sub-cohort of participants the years 1996 to 2014 due to lack of data before year 1996.

4.3.4 Study IV

4.3.4.1 Design

Multinational population-based cohort study that investigated all-cause 90-day mortality, 90-day reoperation, and prolonged hospital stay, following primary laparoscopic or secondary antireflux surgery from year 2000 to 2018.

4.3.4.2 Cohort

This study was based on an updated version of NordASCo, and included all individuals aged ≥18 and ≤80 years with a recorded elective primary laparoscopic antireflux surgery in any of the national patient registries in the five Nordic countries. The update of NordASCo entailed collection of data from the national patient registries and cause of death registries in Finland and Sweden, up to year 2018. A sub-cohort of study participants included those who underwent elective secondary antireflux surgery after having undergone a primary laparoscopic antireflux procedure. Excluded were individuals who underwent antireflux surgery in an emergency setting or those who had surgery following incarcerated hernia. The main outcome was all-cause 90-day postoperative mortality and secondary outcomes were reoperation within 90 days of surgery due to complications, and prolonged hospital stay (≥2 days longer than the median length of hospital stay) after primary laparoscopic or secondary antireflux surgery. Mortality data came from the cause of death registries and length of hospital stay was defined as number of days from date of admission to date of discharge in the national patient registries.

4.3.4.3 Statistical analyses

Frequencies of absolute rates of mortality and reoperation were calculated. Multivariable logistic regression provided ORs with 95% CIs of the outcomes, adjusted for age, sex, comorbidity, hospital volume, and calendar period. A cubic spline model was used to assess the influence of the continuous covariates age, year of surgery, and annual hospital volume on the odds of prolonged hospital stay, adjusted for the other exposures. The results of these were presented in probability graphs with the following reference values: age 43-55 years, male, Charlson Comorbidity Index 0, calendar year 2000-2003, and Finland.

4.4 ETHICAL CONSIDERATIONS

In all Nordic countries, informed consent is not required for registry-based research. While ethical permissions are not required in Denmark and Finland for this type of registry-based research, permissions from relevant ethical committees in Iceland (VSN-14-083), Norway (2014/1498-3) and Sweden have been acquired (2014/234-31, 2015/240-32 and 2019-04509). The data collected from the Nordic patient registries, cancer registries, and cause of death registries were completely de-identified, without possibility of any identifiable personal information, and the merging of the data from the different registries was anonymously performed. Storage of datasets was electronic, on safe servers at Statistics Denmark or Karolinska Institute. Datasets were password protected and access to them was strictly limited to the few researchers involved in the data management and analysis process. Individuals are impossible to identify from the results.

5 RESULTS

5.1 STUDY I

In Study I, 814,230 patients with GERD were included in the cohort, of which 47,016 (5.8%) underwent antireflux surgery. Among the 269,656 patients with severe GERD, 34,766 (12.9%) underwent antireflux surgery.

Table 2. *Characteristics of participants included in Study I.*

Gastroesophageal reflux disease		
	Antireflux surgery Number (%)	**No antireflux surgery Number (%)**
Total		
Patients	47,016 (100)	780,546 (100)
Person-years of follow-up	556,234	5,020,529
Sex		
Male	26,478 (56.3)	378,757 (48.5)
Female	20,538 (43.7)	401,789 (51.5)
Age at inclusion		
<50 years	22,095 (47.0)	256,475 (32.9)
50-<65 years	18,226 (38.8)	237,604 (30.4)
≥65 years	6,695 (14.2)	286,467 (36.7)
Laryngeal or pharyngeal squamous cell carcinoma	39 (0.08)[100]	699 (0.09)[100]
Laryngeal squamous cell carcinoma	20 [51.3]	311 [44.5]
Pharyngeal squamous cell carcinoma	19 [48.7]	388 [55.5]

Severe gastroesophageal reflux disease (reflux esophagitis or Barrett's esophagus)		
	Antireflux surgery Number (%)	**No antireflux surgery Number (%)**
Total		
Patients	34,766 (100)	242,619 (100)
Person-years of follow-up	425,331	1,996,651
Sex		
Male	20,065 (57.7)	133,827 (55.2)
Female	14,701 (42.3)	108,792 (44.8)
Age at inclusion		
<50 years	16,737 (48.1)	76,813 (31.7)
50-<65 years	13,768 (39.6)	76,918 (31.7)
≥65 years	4,261 (12.3)	88,888 (36.6)
Laryngeal or pharyngeal squamous cell carcinoma	28 (0.08)[100]	321 (0.13)[100]
Laryngeal squamous cell carcinoma	12 [42.9]	148 [46.1]
Pharyngeal squamous cell carcinoma	16 [57.1]	173 [53.9]

Table 2 shows some characteristics of the study participants. Among participants with GERD, 39 (0.08%) were identified with laryngeal or pharyngeal squamous cell carcinoma in the antireflux surgery group during follow-up, and 699 (0.09%) in the non-operated group. Among those with severe GERD (sub-cohort), 28 (0.08%) and 321 (0.13%) were identified with these tumors in the antireflux surgery group and the non-operated group, respectively.

Comparing operated patients with GERD with the corresponding background population, a decrease in the overall SIRs was seen for laryngeal or pharyngeal squamous cell carcinoma (SIR 0.62, 95% CI 0.44-0.85), and after more than 10 years of follow-up, the point estimate was further reduced (SIR 0.48, 95% CI 0.26-0.80) (Table 3). When analyzed separately, the overall SIR was decreased for laryngeal squamous cell carcinoma (SIR 0.65, 95% CI 0.40-1.00) and pharyngeal squamous cell carcinoma (SIR 0.60, 95% CI 0.36-0.93). The SIR reduced further after more than 10 years of follow-up for laryngeal squamous cell carcinoma (SIR 0.28, 95% CI 0.08-0.72), but no such decrease over time was observed for pharyngeal squamous cell carcinoma (Table 3). Non-operated patients with GERD had similar incidence of laryngeal or pharyngeal squamous cell carcinoma (analyzed combined and separately) to that of the corresponding background population (Table 3). The analyses of patients of the sub-cohort with severe GERD yielded similar results to that of the main cohort.

Table 3. *SIRs and 95% CIs of laryngeal and pharyngeal squamous cell carcinoma (SCC) in GERD patients compared to the background population.*

	Laryngeal or pharyngeal SCC		**Laryngeal SCC**		**Pharyngeal SCC**	
Follow-up (years)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
			Antireflux surgery			
>1-34	39	0.62 (0.44-0.85)	20	0.65 (0.40-1.00)	19	0.60 (0.36-0.93)
>1-5	8	0.54 (0.23-1.07)	5	0.67 (0.22-1.57)	3	0.41 (0.08-1.20)
>5-10	17	0.91 (0.53-1.45)	11	1.20 (0.60-2.14)	6	0.63 (0.23-1.37)
>10	14	0.48 (0.26-0.80)	4	0.28 (0.08-0.72)	10	0.67 (0.32-1.23)
			No antireflux surgery			
>1-34	699	1.00 (0.93-1.08)	311	0.94 (0.84-1.05)	388	1.06 (0.96-1.17)
>1-5	305	1.05 (0.94-1.17)	133	0.95 (0.79-1.12)	172	1.15 (0.98-1.33)
>5-10	212	0.99 (0.87-1.14)	99	0.99 (0.80-1.20)	113	1.00 (0.83-1.20)
>10	182	0.95 (0.81-1.09)	79	0.88 (0.70-1.10)	103	1.00 (0.82-1.21)

Comparing operated patients with non-operated patients with GERD, the overall adjusted HR was decreased for laryngeal or pharyngeal squamous cell carcinoma (HR 0.55, 95% CI 0.38-0.80), and a slight further reduction of the point estimate was observed after more than 10 years of follow-up (HR 0.47, 95% CI 0.26-0.85) (Table 4). In the separate analyses of the

tumor types, the overall adjusted HR was decreased for laryngeal (HR 0.53, 95% CI 0.31-0.90) and pharyngeal (HR 0.58, 95% CI 0.35-0.96) squamous cell carcinoma. The HRs further decreased after more than 10 years of follow-up for laryngeal squamous cell carcinoma (HR 0.23, 95% CI 0.08-0.69), but not for pharyngeal squamous cell carcinoma (Table 4). The analyses of patients of the sub-cohort with severe GERD yielded mainly similar results to that of the main cohort.

Table 4. *Risk of laryngeal and pharyngeal squamous cell carcinoma (SCC) in GERD patients who had antireflux surgery or not, presented as HRs with 95% CIs.*

	No antireflux surgery		**Antireflux surgery**		
Follow-up (years)	Cases (n)	HR (95% CI)	Cases (n)	Crude HR (95% CI)	Adjusted ǂ HR (95% CI)
			Laryngeal or pharyngeal SCC		
>1-34	699	1.00 (Reference)	39	0.48 (0.34-0.66)	0.55 (0.38-0.80)
>1-5	305	1.00 (Reference)	8	0.36 (0.18-0.73)	0.36 (0.16-0.82)
>5-10	212	1.00 (Reference)	17	0.68 (0.41-1.11)	0.92 (0.53-1.60)
>10	182	1.00 (Reference)	14	0.40 (0.23-0.69)	0.47 (0.26-0.85)
			Laryngeal SCC		
>1-34	311	1.00 (Reference)	20	0.55 (0.35-0.87)	0.53 (0.31-0.90)
>1-5	133	1.00 (Reference)	5	0.52 (0.21-1.27)	0.43 (0.15-1.25)
>5-10	99	1.00 (Reference)	11	0.94 (0.51-1.76)	1.17 (0.57-2.41)
>10	79	1.00 (Reference)	4	0.26 (0.10-0.71)	0.23 (0.08-0.69)
			Pharyngeal SCC		
>1-34	388	1.00 (Reference)	19	0.42 (0.26-0.66)	0.58 (0.35-0.96)
>1-5	172	1.00 (Reference)	3	0.24 (0.08-0.75)	0.30 (0.08-1.09)
>5-10	113	1.00 (Reference)	6	0.45 (0.20-1.02)	0.69 (0.29-1.64)
>10	103	1.00 (Reference)	10	0.52 (0.27-0.99)	0.72 (0.36-1.46)

ǂ Adjusted for sex, age (continuous), calendar period, country, chronic obstructive pulmonary disease, obesity (including diabetes mellitus type 2) and history of excessive alcohol consumption.

5.2 STUDY II

Study II included 812,617 participants with GERD, of which 46,996 (5.8%) underwent antireflux surgery. During follow-up, lung cancer was identified in 3,650 (0.5%) and 273 (0.6%) patients in the non-operated group and in the antireflux surgery group, respectively. Among the 269,318 of participants with severe GERD (sub-cohort), 34,752 (12.9%) underwent antireflux surgery. Lung cancer was identified in 1,491 (0.6%) patients in the non-operated group and in 191 (0.5%) patients in the antireflux surgery group.

Comparing operated patients with GERD to the corresponding background population, a decrease in the overall SIRs was observed for small cell carcinoma (SIR 0.57, 95% CI 0.41-0.77) and squamous cell carcinoma (SIR 0.75, 95% CI 0.60-0.92), but not for adenocarcinoma (SIR 0.90, 95% CI 0.76-1.06) of the lung (Table 5). The SIRs did not decrease with longer follow-up. Patients of the sub-cohort with severe GERD had similar results to that of the main cohort.

Comparing non-operated patients with GERD to the corresponding background population, a decrease in the overall SIRs was seen for all three histological types of lung cancer, and the SIRs did not change much over time (Table 5). Similar results were observed for severe GERD.

Table 5. *SIRs and 95% CIs of lung cancer by histological type in GERD patients compared to the background population.*

	Small cell carcinoma		**Squamous cell carcinoma**		**Adenocarcinoma**	
Follow-up (years)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
			Antireflux surgery			
>1-34	43	0.57 (0.41-0.77)	88	0.75 (0.60-0.92)	142	0.90 (0.76-1.06)
>1-5	14	0.75 (0.41-1.26)	16	0.59 (0.34-0.95)	24	0.74 (0.47-1.09)
>5-10	7	0.31 (0.12-0.64)	25	0.73 (0.47-1.08)	42	0.94 (0.68-1.27)
>10-15	11	0.62 (0.31-1.11)	19	0.67 (0.40-1.05)	40	1.00 (0.72-1.37)
>15	11	0.68 (0.34-1.22)	28	1.00 (0.66-1.44)	36	0.89 (0.62-1.23)
			No antireflux surgery			
>1-34	724	0.83 (0.77-0.89)	1152	0.87 (0.82-0.92)	1774	0.83 (0.80-0.87)
>1-5	332	0.86 (0.77-0.96)	550	0.95 (0.87-1.03)	786	0.88 (0.82-0.94)
>5-10	200	0.77 (0.67-0.89)	322	0.81 (0.73-0.91)	562	0.87 (0.80-0.95)
>10-15	114	0.82 (0.67-0.98)	160	0.76 (0.64-0.88)	274	0.76 (0.68-0.86)
>15	78	0.88 (0.69-1.10)	120	0.87 (0.72-1.04)	152	0.67 (0.57-0.79)

Compared to non-operated patients with GERD, those who underwent antireflux surgery had decreased adjusted HRs for small cell carcinoma (HR 0.63, 95% CI 0.44-0.90), decreased point estimate for squamous cell carcinoma (HR 0.80, 95% CI 0.62-1.03), and no decreased risk of adenocarcinoma (HR 1.03, 95% CI 0.84-1.26). No further decrease of the HRs over longer follow-up time was observed for any of the histological types (Table 6).

Table 6. *Risk of lung cancer by histological type in GERD patients who had antireflux surgery or not, presented as HRs with 95% CIs.*

	No antireflux surgery		Antireflux surgery		
Follow-up (years)	Cases (n)	HR (95% CI)	Cases (n)	Crude HR (95% CI)	Adjusted[ǂ] HR (95% CI)
			Small cell carcinoma		
>1-34	724	1.00 (Reference)	43	0.51 (0.37-0.69)	0.63 (0.44-0.90)
>1-5	332	1.00 (Reference)	14	0.58 (0.34-0.99)	0.81 (0.44-1.49)
>5-10	200	1.00 (Reference)	7	0.30 (0.14-0.64)	0.37 (0.16-0.89)
>10-15	114	1.00 (Reference)	11	0.57 (0.31-1.06)	0.66 (0.32-1.37)
>15	78	1.00 (Reference)	11	0.62 (0.33-1.17)	0.71 (0.37-1.38)
			Squamous cell carcinoma		
>1-34	1152	1.00 (Reference)	88	0.66 (0.53-0.82)	0.80 (0.62-1.03)
>1-5	550	1.00 (Reference)	16	0.40 (0.24-0.66)	0.58 (0.33-1.03)
>5-10	322	1.00 (Reference)	25	0.67 (0.44-1.00)	0.74 (0.45-1.21)
>10-15	160	1.00 (Reference)	19	0.71 (0.44-1.14)	0.86 (0.50-1.49)
>15	120	1.00 (Reference)	28	1.02 (0.68-1.54)	1.13 (0.72-1.77)
			Adenocarcinoma		
>1-34	1774	1.00 (Reference)	142	0.70 (0.58-0.82)	1.03 (0.84-1.26)
>1-5	786	1.00 (Reference)	24	0.42 (0.28-0.62)	0.83 (0.52-1.32)
>5-10	562	1.00 (Reference)	42	0.64 (0.47-0.87)	1.07 (0.74-1.54)
>10-15	274	1.00 (Reference)	40	0.88 (0.63-1.22)	1.09 (0.73-1.62)
>15	152	1.00 (Reference)	36	1.05 (0.73-1.51)	1.12 (0.75-1.67)

ǂ Adjusted for sex, age (continuous), calendar period, country, obesity diagnosis, diabetes mellitus type 2, and chronic obstructive pulmonary disease.

5.3 STUDY III

In Study III, 240,226 participants were identified with reflux esophagitis or Barrett's esophagus. Table 7 shows some characteristics of the study participants. Among all participants, 33,904 (14.1%) had undergone antireflux surgery. In the antireflux medication group, 39,390 (19.1%) died of any cause, and in the antireflux surgery group, 4,496 (13.3%) died of any cause.

Table 7. *Characteristics of participants included in Study III.*

	Antireflux surgery Number (%)	Antireflux medication Number (%)
Patients	33,904 (100)	206,322 (100)*
Person-years	445,594 (100)	1,851,087 (100)
Sex		
Men	19,757 (58.3)	119,255 (57.8)
Women	14,147 (41.7)	87,067 (42.2)
Age at inclusion		
<50 years	16,927 (49.9)	86,221 (41.8)
50-<65 years	13,959 (41.2)	86,517 (41.9)
≥65 years	3,018 (8.9)	33,584 (16.3)
Charlson Comorbidity Index score		
0	31,172 (91.9)	173,499 (84.1)
1	2,466 (7.3)	25,403 (12.3)
≥2	266 (0.8)	7,420 (3.6)
Surgical approach (1996 – 2014)ǂ		
Any approach	23,656 (69.8) [100]	Not applicable
Laparoscopic approach	21,231 [89.7)	Not applicable
Open approach	2,332 [9.9]	Not applicable
Converted to open	93 [0.4]	Not applicable
Causes of mortality		
All causes	4,496 (13.3)	39,390 (19.1)
Cardiovascular diseases	2,159 (6.4)	19,102 (9.3)
Respiratory diseases	1,154 (3.4)	10,229 (5.0)
Esophageal cancer	158 (0.5)	964 (0.5)
Laryngeal or pharyngeal cancer	13 (0.0)	270 (0.1)
Lung cancer	257 (0.8)	2,253 (1.1)

* Among the non-operated patients, 20,272 were included in the operated group after they were censored from the non-operated group at the date of admission to antireflux surgery.
ǂ Restricted to the study period 1996-2014, from which data on antireflux surgery approach were available.

The comparison of participants in the antireflux surgery group with those in the antireflux medication group is shown in Table 8. Comparing antireflux surgery with medication, the adjusted risk of all-cause mortality was decreased (HR 0.61, 95% CI 0.58-0.63), and remained decreased over time. The adjusted risk of all-cause mortality risk was similarly decreased between sexes and age groups, but more decreased in participants with comorbidity (HR 0.47 [95% CI 0.37-0.58] for Charlson comorbidity score ≥2) compared to participants without comorbidity (HR 0.62 [95% CI 0.59-0.64] for Charlson comorbidity score 0).

Comparing antireflux surgery with antireflux medication with regards to disease-specific mortality, the adjusted overall HRs were decreased for mortality from cardiovascular disease (HR 0.58, 95% CI 0.55-0.61), respiratory disease (HR 0.62, 95% CI 0.57-0.66), laryngeal or pharyngeal cancer (HR 0.35, 95% CI 0.19-0.65), and lung cancer (HR 0.67, 95% CI 0.58-0.80), but not from esophageal cancer (HR 1.05, 95% CI 0.87-1.28). The reduced HRs stayed decreased over time, and the HR was particularly decreased for laryngeal or pharyngeal cancer after more than 15 years of follow-up (HR 0.18, 95% CI 0.04-0.81).

5.4 STUDY IV

In Study IV, 26,193 patients had undergone elective primary laparoscopic antireflux surgery for GERD, and 1,618 patients also underwent elective secondary antireflux surgery.

The absolute rate of 90-day mortality was 0.13% (n=35) after primary laparoscopic antireflux surgery and 0.19% (n=3) after secondary antireflux surgery. Cardiovascular disease and suicide or intoxication were the most common causes of death. The ORs of 90-day all-cause mortality and 90-day reoperation following primary laparoscopic antireflux surgery are presented in Table 9. The adjusted ORs of 90-day mortality increased in participants with higher age (highest vs lowest tertile: OR 2.66, 95% CI 1.03-6.85) and in participants with comorbidity (Charlson Comorbidity Index ≥2 vs 0: OR 6.25, 95% CI 2.42-16.14). The risk

Table 8. *All-cause mortality in patients with reflux esophagitis or Barrett's esophagus comparing antireflux surgery with medication, presented as HRs with 95% CIs.*

	No antireflux surgery		**Antireflux surgery**		
All-cause mortality	Deaths (n)	HR (95% CI)	Deaths (n)	Crude HR (95% CI)	Adjusted[ł] HR (95% CI)
Follow-up (years)					
0-34	39,390	1.00 (Reference)	4,496	0.46 (0.45-0.48)	0.61 (0.58-0.63)
>1-5	15,697	1.00 (Reference)	784	0.26 (0.24-0.28)	0.41 (0.38-0.45)
>5-10	9,121	1.00 (Reference)	991	0.43 (0.40-0.46)	0.54 (0.50-0.58)
>10-15	6,871	1.00 (Reference)	1,116	0.53 (0.50-0.57)	0.63 (0.59-0.68)
>15	7,701	1.00 (Reference)	1,605	0.71 (0.67-0.75)	0.76 (0.72-0.81)
Sex					
Men	25,936	1.00 (Reference)	2,901	0.44 (0.42-0.45)	0.59 (0.56-0.61)
Women	13,454	1.00 (Reference)	1,595	0.51 (0.48-0.53)	0.64 (0.61-0.68)
Age at inclusion (years)					
<50	7,771	1.00 (reference)	1,125	0.53 (0.50-0.57)	0.62 (0.57-0.66)
50-<65	18,511	1.00 (reference)	2,255	0.48 (0.45-0.50)	0.59 (0.56-0.62)
≥65	13,108	1.00 (reference)	1,116	0.56 (0.53-0.60)	0.65 (0.61-0.70)
Charlson Comorbidity Index score					
0	25,430	1.00 (reference)	3,905	0.56 (0.54-0.58)	0.62 (0.59-0.64)
1	9,765	1.00 (reference)	505	0.38 (0.35-0.42)	0.48 (0.44-0.53)
≥2	4,195	1.00 (reference)	86	0.37 (0.30-0.46)	0.47 (0.37-0.58)

ł Adjusted for sex, age, calendar period, country of residence, and Charlson Comorbidity Index score (excluding the variable analyzed).

was not influenced by sex. Although not statistically significant, the point estimates of higher hospital volume were decreased (highest vs lowest tertile: OR 0.58, 95% CI 0.22-1.57).

The 90-day reoperation rate was 3.0% (n=750) after primary laparoscopic antireflux surgery and 6.2% (n=94) after secondary antireflux surgery. Comparing greater Charlson comorbidity index scores with score of 0, the OR of 90-day reoperation was increased (Charlson Comorbidity Index ≥2 vs 0: OR 1.47, 95% CI 0.97-2.23; and Charlson Comorbidity Index 1 vs 0: OR 1.29, 95% CI 1.05-1.58)) within 90 days of primary laparoscopic antireflux surgery (Table 9). No such pattern was observed within 90 days of secondary antireflux surgery, and there were no statistically significant associations between age, calendar period, sex, hospital volume and risk of reoperation within 90 days following both primary laparoscopic and secondary antireflux surgery.

Table 9. *ORs and 95% CIs of 90-day mortality and 90-day reoperation after primary laparoscopic antireflux surgery.*

	90-day mortality		90-day reoperation	
	Cases (n)	Adjusted ǂ OR (95% CI)	Cases (n)	Adjusted ǂ OR (95% CI)
Age (in years)				
18-42	6	1.00 (Reference)	241	1.00 (Reference)
43-55	6	0.87 (0.28-2.73)	245	0.92 (0.78-1.11)
56-80	23	2.66 (1.03-6.85)	264	0.98 (0.81-1.18)
Sex				
Male	15	1.00 (Reference)	389	1.00 (Reference)
Female	20	1.08 (0.54-2.14)	361	1.04 (0.89-1.20)
Charlson Comorbidity Index				
0	21	1.00 (Reference)	608	1.00 (Reference)
1	8	1.93 (0.84-4.44)	117	1.29 (1.05-1.58)
≥2	6	6.25 (2.42-16.14)	25	1.47 (0.97-2.23)
Annual hospital volume‖				
≤24	13	1.00 (Reference)	252	1.00 (Reference)
25-47	14	0.99 (0.43-2.25)	224	0.84 (0.70-1.02)
>47	6	0.58 (0.22-1.57)	252	1.10 (0.91-1.32)
Calendar period (in years)				
2000 – 2003	6	1.00 (Reference)	229	1.00 (Reference)
2004 – 2008	10	1.51 (0.55-4.20)	246	1.07 (0.89-1.29)
2009 – 2018	19	2.33 (0.91-5.98)	275	1.15 (0.95-1.38)

* Two or more days longer than the median length of hospital stay after surgery.
ǂ Adjusted for age, sex, Charlson Comorbidity Index, calendar period, and country.
‖ Restricted to 23,690 participants from Denmark, Finland, and Sweden with data on hospital volume.

Following primary laparoscopic and secondary antireflux surgery, the median length of hospital stay was 3 days (IQR 2-4 days) and 4 days (IQR 2-6 days), respectively. Among participants in the primary and secondary antireflux surgery groups, 5,252 (20%) and 477 (29%) had prolonged hospital stay, respectively. Among participants in the primary laparoscopic antireflux surgery group, an increased risk of prolonged hospital stay was seen with higher age (upward deflection after 60 years of age), and a decreased risk of prolonged hospital stay was seen with greater hospital volume (Figure 5). In the early calendar years of the study, an initial decrease in risk of prolonged hospital stay was observed, which remained stable over time (Figure 5).

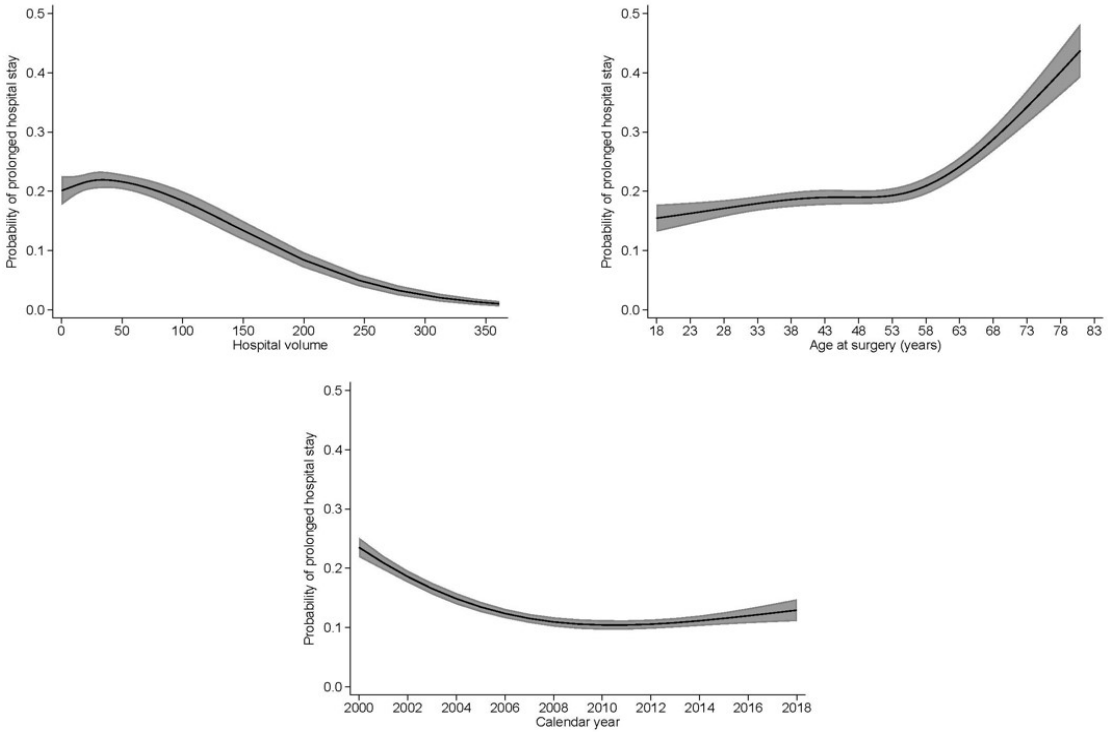

Figure 5. *Probability (black line) with 95% CIs (grey area) of prolonged hospital stay by hospital volume, age and calendar year after primary laparoscopic antireflux surgery.*

The OR of prolonged hospital stay was increased for males compared to females (OR 1.48, 95% CI 1.37-1.61), and increased with higher Charlson comorbidity score compared to no comorbidity (OR 1.54 [95% CI 1.40-1.68] with a score of 1 and OR 2.38 [95% CI 1.98-2.85] with a score of ≥2). Similar results were seen in the secondary antireflux surgery group, except for sex and hospital volume, which did not influence the OR of prolonged hospital stay.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

All studies in the present thesis are population-based cohort studies from the Nordic countries. Cohort studies comprise individuals from a source population, selected based on one or several pre-specified exposures, who are followed over time to assess outcomes of interest. A strength of studies I-IV is the population-based design, encompassing essentially all individuals who have a documented diagnosis of GERD or antireflux surgery procedure, and meeting the inclusion criteria of each study, in any of the five Nordic countries. This provided an unselected cohort. A long-term and virtually complete follow-up of all cohort participants was made possible by the well-maintained nationwide health data registries, in which all individuals are traceable by a personal identity number, uniquely available in the Nordic countries. This design abated selection bias, minimized loss to follow-up, and provided a large sample size, which is needed to enable assessment of rare outcomes. In general, weaknesses to consider in observational studies pertain to internal and external validity. The key biases that determine the internal validity of observational studies are selection bias, information bias, and confounding. Another source of error is chance (random error).

6.1.2 Internal validity

6.1.2.1 Selection bias

Selection bias is a differential error that can occur when selection and inclusion of participants in a study result in a systematic difference between the sample population and the source population. This can yield study results that cannot be transferred to the source population. Lack of participation, or self-selection bias, is not likely to have significantly contributed to selection bias in Study I-IV because almost all patients in the five Nordic countries were included. Nonetheless, in clinical practice, the likelihood of patients receiving a diagnosis of GERD may vary depending on the main cause of seeking healthcare. Therefore, participation in Study I-III might have been affected by local traditions of hospitals and outpatient clinics. However, this is likely to mainly affect individuals with mild GERD. Moreover, local traditions should not affect the documentation of antireflux surgery in the national patient registries. Another possible contribution to selection bias is that individuals with mild GERD might never be diagnosed because not all patients seek healthcare for their GERD-symptoms, or are managed solely in a primary care setting. These individuals do not meet the inclusion criteria of Study I-III, i.e. documented diagnosis of GERD in the national patient registries. However, this should not have had a strong influence on the internal validity of Study I-III, where it was more important that the GERD diagnosis was accurate than including more ill-defined GERD diagnoses, which could have introduced substantial information bias.

6.1.2.2 Information bias

Information bias occurs when measurements or classifications of one or more exposures or outcomes in a study are inaccurate. Differential misclassification occurs when measurement errors lead to a misclassification of exposure or outcome that differs between the comparison groups. Non-differential misclassification occurs when measurement errors lead to a misclassification of exposure or outcome that do not differ between the comparison groups. Misclassification of exposures can be considered limited in all studies in the present thesis. Nonetheless, in Study I-II, some misclassification of GERD diagnosis is possible in participants who received a clinical GERD diagnosis without objective confirmation (by endoscopic assessment). However, the sub-analyses of participants with objectively determined GERD in these studies showed similar results compared to the main analyses, which suggests that misclassification of GERD was limited. Furthermore, Study III was restricted to participants with objectively confirmed GERD only. Misclassification of antireflux surgery should be low or absent considering the existence of universal health care systems, mandatory reporting of surgical procedures, and reimbursement dependent on this reporting in the Nordic countries. Recurrence of GERD following antireflux surgery is not uncommon, and has been shown to occur in 17.7% of the Swedish cohort participants,(47) which could be seen as a kind of exposure misclassification in Study I-III. This misclassification could have affected the results toward null values. Misclassification of outcomes (malignancy, death date and cause of death) in Study I-IV can also be considered low given the high completeness and validity of the national cancer registries and cause of death registries in the Nordic countries.

6.1.2.3 Random error

Random error, or chance variation, is the divergence of statistical measurements in a sample from the true value in the source population, due to chance. This error is the inverse of statistical precision. All study populations, including those that are national population-based, are considered to be sampled from a super-population. Therefore, random errors cannot be entirely avoidable. An effective approach to counteract random error is the use of large sample sizes and avoidance of multiple testing. Therefore, the use of a multinational population-based cohort in Study I-IV decreased the risk of random errors and increased statistical precision. In statistical analyses, common measurements of point estimate precision include calculation of CIs or P-values. The CIs are usually set at 95%, which represents a 95% confidence that the true value in the super population lies within the calculated interval, given no influence of any bias. The P-values are usually set at a significance level of $\leq$0.05, which represents a less than 5% probability of finding a difference between comparison groups in a sample population when no true difference exists in the super-population. This is commonly referred to as the probability of Type-I error or false rejection of the null hypothesis. Type-I errors can be counteracted by reducing significance testing or correcting for multiple testing. However, these strategies usually increase the risk of Type-II errors (non-rejection of a false null-hypothesis), i.e. observing no difference between comparison groups in a sample population when a true difference exists in the super-population. In this

thesis, multiple testing was reduced by using limited predefined study hypotheses and only including covariates based on subject-matter knowledge. Furthermore, in all studies of the present thesis, only 95% CIs were used for assessment of statistical precision and significance, which is mostly more informative than P-values because the CIs also provide information on strength and direction of effect.

6.1.2.4 Confounding

Confounding might occur when a factor is independently associated with both the exposure and outcome, and is not a mediator, i.e. not in the causal pathway between the exposure and outcome. The presence of confounding is commonly a challenge in observational studies, because they are not randomized, and if not sufficiently counteracted, it can account for some or all of the associations found in such studies. In observational studies, confounding can be counteracted in the study design phase by matching study participants based on variables that could introduce confounding, or in the statistical analyses by adjusting or stratifying for such variables. The main approach to reduce confounding in the studies of the present thesis was by using multivariable regression models, in which adjustments and stratifications were made. The covariates selected for inclusion in the models was based on subject-matter knowledge. In some cases, direct data on relevant covariates that could introduce confounding was not available. These were instead indirectly accounted for by capturing proxy indicators, i.e. indicators that are closely related to the possibly confounding covariates. Nonetheless, residual or unmeasured confounding is a limitation in each of the studies included in the thesis.

6.1.3 External validity

External validity, also called generalizability, pertains to the possibility of inferring results from a study population to other populations and settings. While internal validity is not affected by external validity, it is very difficult to discuss generalization when the internal validity is poor. Study I-IV were all multinational and population-based, encompassing nationwide participation in the Nordic countries. This should have facilitated high generalizability to other Western populations at least.

6.2 GENERAL DISCUSSION

6.2.1 Study I

Study I suggests that the risk of laryngeal and pharyngeal squamous cell carcinoma is decreased in patients with GERD who have had antireflux surgery compared to the corresponding background population and to patients with GERD who have not undergone such surgery.

Strengths of Study I are the population-based design and the long and complete follow-up of a large sample size. Analyses of the sub-cohort of severe GERD (objectively determined) decreased risk of misclassification of GERD, and the similar results provided more validity to the analyses of the main cohort. Among weaknesses was possible confounding. The main

shared risk factors for laryngeal and pharyngeal squamous cell carcinoma, and GERD, are tobacco smoking and heavy alcohol consumption, and to a less extent obesity.(3, 143, 144) It was not possible to adjust for these factors in the SIR-analyses, but they were controlled for in the Cox regression analyses. However, direct information on tobacco smoking and alcohol consumption are not available in the national patient registries, but were instead adjusted for through proxies, which should have counteracted confounding. Finally, despite the large cohort size, the power of the analyses was limited due to low incidence of the tumor types under study.

No other study has assessed the influence of antireflux surgery on the risk of laryngeal or pharyngeal cancer. The observed decrease in risk of laryngeal and pharyngeal squamous cell carcinoma after antireflux surgery indicates that these tumors can be counteracted in patients with GERD. Another explanation could be that individuals who are selected for surgery might be less likely to be heavy tobacco smokers or alcohol consumers compared to the corresponding background population and to non-operated patients with GERD. Nonetheless, these factors were indirectly adjusted for in the analyses. Furthermore, in a recent meta-analysis, the risk of laryngeal cancer risk was found to be increased by GERD after controlling for direct measures of tobacco smoking and alcohol intake.(93) In addition, the point estimates of laryngeal squamous cell carcinoma was further decreased over time, following antireflux surgery, which is not likely explained by selection to surgery.

Chronic inflammation and repeated inflammatory insults have been associated with several cancer types in the aerodigestive tract,(145-149) and an association between GERD and laryngeal and pharyngeal cancer has been suggested in several studies.(88-94) The epithelium of larynx and pharynx seems to be vulnerable to repeated inflammatory insults from acidic and non-acidic duodeno-gastric contents.(63-67, 93) Therefore, the development of laryngeal and pharyngeal cancer might be counteracted by means of the mechanic and physiologic barrier that is created with antireflux surgery, which hinders both acidic and non-acidic refluxate, in contrast to antireflux medication, which only reduces the acidic component of refluxate.(25) The finding of no association between GERD and laryngeal and pharyngeal squamous cell carcinoma in Study I was not expected. An explanation could be that antireflux medication had some cancer-preventive effects, which is typically used in non-operated patients with GERD. Another explanation could be that compared to the background population, those who are diagnosed with GERD are more prone to reduce tobacco smoking and alcohol intake.

6.2.2 Study II

Study II suggests that compared to the corresponding background population and non-operated patients with GERD, patients with GERD who have undergone antireflux surgery have a decreased risk of small cell carcinoma and squamous cell carcinoma, but not of adenocarcinoma of the lung.

The methodological strengths of Study II include the large sample size, population-based design, and the long and complete follow-up. The similarity in the results of the main and sub-cohort suggests that misclassification of GERD was low. Among weaknesses is possible confounding. The main shared risk factor for the lung cancer tumor types and GERD is tobacco smoking.(3, 150) While direct data on tobacco smoking was not available, adjustment for chronic obstructive pulmonary disease was performed, which has a strong association to duration of smoking and intensity.(151) Furthermore, in a study assessing esophageal adenocarcinoma, using the same cohort as in Study II, antireflux surgery did not influence the risk, which indicates that selection of patients with GERD to surgery introduces limited bias compared to the non-operated group and the background population.(87) The findings of this study could be generalized to other Western populations, where the prevalence of GERD is similar.(4, 5)

No previous study has assessed the risk of lung cancer following antireflux surgery in patients with GERD. The findings suggest that antireflux surgery decreases the risk of small cell carcinoma and squamous cell carcinoma. Because no further decrease in risk could be observed over time after antireflux surgery, careful interpretation of the results is necessary. The lack of risk reduction over time could nonetheless be explained by recurrence of GERD after surgery. Future studies are required to confirm these findings. Nevertheless, a possible biologic explanation to these findings is that antireflux surgery mechanically hinders acidic and non-acidic duodeno-gastric reflux, which leads to a reduction of micro-aspiration, repeated inflammatory insults, and subsequent oncogenic processes in tissues of the lung. Since antireflux medication does not hinder proximal reflux, but only reduces its acidity, the finding of a decreased risk of lung cancer following antireflux surgery compared to non-operated patients with GERD (vastly using antireflux medication) was expected.

A possible explanation for the findings of a reduction in risk for small cell carcinoma and squamous cell carcinoma, but not of adenocarcinoma, after antireflux surgery could be due to anatomical differences of the histologic types. Small cell carcinoma and squamous cell carcinoma mainly arise in the central airways, while adenocarcinoma primarily arise in the peripheral airways, which is further away from possible micro-aspirations.

6.2.3 Study III

Study III indicates that in patients with reflux esophagitis or Barrett's esophagus, antireflux surgery decreases mortality from all causes, cardiovascular disease, respiratory disease, laryngeal or pharyngeal cancer, and lung cancer, but not from esophageal cancer, compared to antireflux medication.

Among methodological strengths are again the population-based design, large sample size, and long and complete follow-up. Misclassification of GERD was counteracted by only including patients with objectively identified GERD, i.e. reflux esophagitis and Barrett's esophagus. Among weaknesses is confounding. Compared to non-operated patients with GERD, patients selected for antireflux surgery might have been more fit, less obese, and have

less comorbidity and tendency of being heavy smokers or alcohol consumers. To counteract this, adjustment for Charlson Comorbidity Index was performed for diagnoses closely related to obesity, tobacco smoking and heavy alcohol consumption, such as diabetes type II, chronic obstructive pulmonary disease and liver disease.(151-153) Furthermore, the analyses restricted to patients with Charlson Comorbidity Index score of 0 also showed a decreased mortality. Confounding was also assessed in a sensitivity analysis of colon cancer risk in patients with GERD, a cancer type that is not associated with GERD or its treatment. Compared to the antireflux medication group, the analyses showed no reduction in risk of colon cancer in the antireflux surgery group (HR 1.16, 95% CI 1.01-1.33). The limited availability of data on antireflux medication is another limitation. However, virtually all non-operated participants with reflux esophagitis or Barrett's esophagus included in the large validation study were shown to be using antireflux medication, which also reflects practice guidelines.(27)

The few previous studies assessing antireflux surgery's influence on survival in patients with GERD have shown conflicting results. .(57, 58) These studies were smaller in sample size and had shorter follow-up. The finding of lower mortality after antireflux surgery could be due to antireflux surgery creating a barrier that counteract both acidic and non-acidic reflux, which might reduce the risk of extra-esophageal diseases that may influence survival, and are associated with GERD, i.e. idiopathic pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease.(60, 68, 154, 155) An alternative explanation of patient selection, as discussed above, cannot be entirely ruled out. Healthy and fit individuals who require a less technically demanding antireflux surgery are likely to be selected for laparoscopic rather than open surgery. This might explain the finding of a more pronounced decrease in mortality in patients who underwent laparoscopic antireflux surgery, compared to open surgery. A recent multinational population-based study (from our group) showed no decreased risk in esophageal adenocarcinoma after antireflux surgery, which supports this study's finding that antireflux surgery does not influence mortality from esophageal cancer.(87) Furthermore, Study I of this thesis suggests that antireflux surgery might decrease the risk of laryngeal and pharyngeal squamous cell carcinoma, which is in line with this study's finding that antireflux surgery decreases mortality from these tumors.

6.2.4 Study IV

Study IV found low 90-day mortality and reoperation rates, as well as a short median hospital stay following primary elective laparoscopic and secondary antireflux surgery. For laparoscopic antireflux surgery, the risk of 90-day mortality increased with comorbidity, higher age, and lower annual hospital volume, and the risk of 90-day reoperation increased with comorbidity, while the risk of prolonged hospital volume increased with comorbidity and higher age, and decreased with male sex, higher hospital volume, and later calendar period. For secondary antireflux surgery, the risk of prolonged hospital stay was increased by comorbidity and higher age, and decreased with later calendar periods.

Among the strengths of this study is the multinational population-based design and complete follow-up of participants, encompassing virtually all individuals who have had primary laparoscopic or secondary antireflux surgery during the study period. Weaknesses include residual or unmeasured confounding. Higher BMI and tobacco smoking can lead to increased risk of postoperative complications. These factors were only indirectly accounted for with the adjustment of Charlson Comorbidity Index. Furthermore, although the sample size was large, the power of some sub-analyses was low.

The absolute rate of all-cause 90-day mortality after primary laparoscopic and secondary antireflux surgery was similar to some other studies.(35, 50) To our knowledge, no previous study has explored risk factors of short-term postoperative mortality following antireflux surgery, which is likely because of the low 90-day mortality rates. Higher age (above 60 years) and comorbidity increased the risk of 90-day mortality following primary laparoscopic antireflux surgery, while higher hospital volume possibly decreased that risk. The higher frailty and probability of severe postoperative complications in older and comorbid patients, and the greater experience in peri- and postoperative care in high volume centers may explain these associations. This could also explain the findings that higher age and comorbidity increased the risk of prolonged hospital stay and high-volume hospitals decreased that risk, following primary laparoscopic and secondary antireflux surgery.

6.3 IMPLICATIONS AND FUTURE RESEARCH

The risk of laryngeal, pharyngeal, and lung cancer following antireflux surgery has not been previously studied. Therefore, the findings of a reduced risk in laryngeal and pharyngeal squamous cell carcinoma, and in small cell and squamous cell carcinoma of the lung require confirmation in future studies before any clinical recommendations can be made. Furthermore, in view of the low incidence of laryngeal and pharyngeal cancer,[43] this thesis does not suggest recommendation of antireflux surgery for only cancer protective reasons. However, these findings indicate that antireflux surgery is effective in the treatment of more proximal reflux and regurgitation, and contribute to tumor etiology knowledge.

Considering the scarcity of studies that have investigated mortality in patients with GERD who have undergone antireflux surgery, compared to antireflux medication, further investigation is needed to confirm the findings of reduced mortality in those operated, before any clinical recommendations can be made.

Finally, this thesis has demonstrated that antireflux surgery has a favorable safety profile. Nonetheless, while severe complications are rare, they do exist. Reduction of poor short-term outcomes after primary laparoscopic and secondary antireflux surgery is likely accomplished by selection of patients below 60 years of age, without severe comorbidity, and by centralization to high-volume specialized centers.

7 CONCLUSIONS

- In patients with GERD, antireflux surgery might decrease the risk of laryngeal squamous cell carcinoma, and possibly also pharyngeal squamous cell carcinoma.
- Antireflux surgery for GERD seems to reduce the risk of small cell carcinoma and squamous cell carcinoma, but not of adenocarcinoma of the lung.
- In patients with GERD, antireflux surgery compared to antireflux medication seems to decrease the risk of all-cause mortality and mortality from cardiovascular disease, respiratory disease, laryngeal or pharyngeal cancer, and lung cancer, but not from esophageal cancer.
- Primary laparoscopic antireflux surgery and secondary antireflux surgery is an overall safe treatment option in the treatment of GERD.

8 POPULAR SCIENCE SUMMARIES

8.1 POPULAR SCIENCE SUMMARY

8.1.1 Background

Gastroesophageal reflux disease (GERD) is a common condition affecting up to 28% of adults in the Western world and the Middle East, and up to 8% of adults in Asia. It is caused by a dysfunction in the anatomic components surrounding the junction between the stomach and the gullet (esophagus), which causes the content of the stomach to leak through the junction and up into the esophagus, leading to heartburn and regurgitation. GERD is a benign condition, but can sometimes lead to complications such as inflammation in the esophagus and cellular changes in the mucosa of the esophagus (called Barrett's esophagus) that in rare cases can lead to esophageal cancer. Some studies have shown that GERD could also increase the risk of cancer in the larynx, pharynx, and lung, with the proposed mechanism that the stomach content affects these organs by reaching further up, above the esophagus. To treat GERD, antireflux medication is used, mainly proton pump inhibitors (PPI), but an alternative is antireflux surgery. While PPIs act by reducing the acidity of stomach content, antireflux surgery mechanically hinders GERD. The surgical procedure is performed by wrapping a part of the upper stomach around the lower part of the esophagus, thus reducing reflux by tightening the upper orifice of the stomach. No previous studies have investigated whether antireflux surgery reduces the risk of cancer in the larynx, pharynx or lung, and the literature is sparse on whether antireflux surgery, compared to antireflux medication, improves the survival in patients with GERD.

8.1.2 Methods and results

The four studies of this thesis were based on the Nordic antireflux surgery cohort (NordASCo), which includes adult individuals who have a registered diagnosis of GERD or antireflux surgery procedure in the national patient registries of Denmark, Finland, Iceland, Norway or Sweden, in the years 1980 to 2018. NordASCo also includes information from the national cancer registries and the national cause of death registries.

Study I aimed to assess whether antireflux surgery decreases the risk of cancer in the larynx or pharynx of the most common type, i.e. squamous cell carcinoma and Study II examined the risk of different types of lung cancer in patients with GERD. Compared to the background population of the corresponding age sex and calendar year, those who underwent antireflux surgery had an overall decreased risk of laryngeal and pharyngeal squamous cell carcinoma. The risk was further decreased over time in laryngeal squamous cell carcinoma. The risk of small cell and squamous cell carcinoma of the lung was also decreased after antireflux surgery, but no such decrease was found for adenocarcinoma of the lung. The results of the comparison between operated and non-operated patients with GERD showed very similar risk patterns to those described above (both studies).

Study III aimed to investigate whether antireflux surgery influences long-term mortality from any cause, and from causes related to specific diseases. Mortality risk was assessed comparing antireflux surgery with antireflux medication treatment in patients with GERD. The results showed that patients who had undergone antireflux surgery had decreased mortality from any cause, and from cardiovascular disease, respiratory disease, laryngeal or pharyngeal cancer, and lung cancer, but not from esophageal cancer.

Study IV aimed to assess absolute risk and risk factors of death and reoperation due to postoperative complications shortly after (within 90 days) primary laparoscopic antireflux surgery and secondary antireflux surgery, as well as risk and risk factors of prolonged hospital stay. Assessment of primary laparoscopic antireflux surgery included patients with GERD who underwent their first antireflux surgery procedure, and secondary antireflux surgery included those who had previously undergone antireflux surgery and underwent a second operation. This study included adult patients in NordASCo who had undergone antireflux surgery from 2000 to 2018. The study showed a low risk of death (0.13%) and reoperation (3.0%) within 90 days of primary surgery, and a low risk of death (0.19%) and reoperation (6.2%) within 90 days of secondary surgery. The risk of 90-day mortality increased in patients with higher age (particularly in those above 60 years) and with other diseases (comorbidity), and the risk seemed to decrease in those who underwent surgery in specialized centers with high operation volume. The risk of reoperation within 90 days of both primary and secondary surgery increased in patients with greater comorbidity. Patients with higher age and greater comorbidity had an increased risk of prolonged hospital stay after both primary and secondary surgery, and those who underwent primary surgery at specialized high-volume centers had a reduced risk.

8.1.3 Summary

In summary, antireflux surgery is a safe treatment option in the treatment of GERD. This surgery seems to reduce the risk of laryngeal and pharyngeal squamous cell carcinoma, and small cell carcinoma and squamous cell carcinoma of the lung, and also decrease mortality in patients with GERD.

8.2 POPULÄRVETENSKAPLIG SAMMANFATTNING

8.2.1 Bakgrund

Gastroesofageal refluxsjukdom (reflux) finns hos uppemot 28% av den vuxna befolkningen i västvärlden och Mellanöstern, och uppemot 8% av vuxna befolkningen i Asien. Reflux orsakas av nedsatt funktion i vävnaderna runt övergången mellan magsäck och matstrupe, vilket orsakar ett ökat läckage av surt magsäcksinnehåll upp i matstrupen och leder till halsbränna och uppstötningar. Reflux är en godartad sjukdom, men kan ibland leda till komplikationer såsom inflammation i matstrupen och cellförändringar i matstrupen (kallade Barretts esofagus) som i sällsynta fall kan leda till matstrupscancer. Vissa studier har visat att reflux även möjligen kan öka risken för cancer i svalg, struphuvud och lunga. Föreslagen verkningsmekanism är att magsäcksinnehållet påverkar dessa organ genom att nå högre upp, ovanför matstrupen. Reflux behandlas främst med läkemedel, vanligen med protonpumpshämmare, men ett alternativ är operation med så kallad antirefluxkirurgi. Medan protonpumpshämmare verkar genom att sänka surhetsgraden i magsäcksinnehållet, motverkar antirefluxkirurgi reflux mekaniskt. Operationen utförs genom att övre delen av magsäcken fästs runt matstrupens nedre del, vilket medför en åtstramning av magsäcksmunnen med minskad reflux som följd. Inga tidigare studier har undersökt om antirefluxkirurgi minskar risken för cancer i svalg, struphuvud eller lunga, och få studier har utvärderat om antirefluxkirurgi påverkar överlevnaden hos patienter med reflux, jämfört med om de behandlas med läkemedel.

8.2.2 Metoder och resultat

De fyra studierna i denna avhandling har baserats på en nordisk kohort (Nordic antireflux surgery cohort – NordASCo) som består av individer med registrerad refluxdiagnos eller som genomgått antirefluxkirurgi enligt de nationella patientregistren i Danmark, Finland, Island, Norge eller Sverige från år 1980 till 2018. NordASCo innehåller även data från de nationella cancerregistren och dödsorsaksregistren.

Studie 1 undersökte om antirefluxkirurgi minskar risken för cancer (av den dominerande typen skivepitelcancer) i svalg eller struphuvud, medan studie 2 undersökta detta för olika cancertyper i lungan bland patienter med reflux. Jämfört med bakgrundsbefolkningen av motsvarande ålder, kön och kalenderår hade de som genomgått antirefluxkirurgi en minskad risk för skivepitelcancer i svalg och struphuvud, samt för småcellig cancer och skivepitelcancer i lungan, men inte för adenocarcinom i lungan. Resultaten var snarlika i jämförelsen av opererade med icke-opererade patienter med reflux i båda studierna.

Studie 3 utvärderade om antirefluxkirurgi påverkar total dödlighet och sjukdomsspecifik dödlighet. Risken för död jämfördes mellan opererade och icke-opererade patienter med reflux. Resultaten visade att patienter som opererats hade en minskad total dödlighet samt minskad dödlighet i hjärt-kärlsjukdomar, sjukdomar i andningsvägarna, samt cancer i svalg, struphuvud och lunga. Däremot förelåg ingen minskad dödlighet i matstrupscancer.

Studie 4 undersökte risk och riskfaktorer för död och behov av omoperation pga. komplikationer inom 90 dagar efter primär (första gången) antirefluxkirurgi med titthålsteknik och sekundär (andra gången) antirefluxkirurgi, och även risken för förlängd sjukhusvistelse efter dessa ingrepp. Studien inkluderade vuxna patienter som hade genomgått antirefluxkirurgi från år 2000 till 2018 i NordASCo. Studien fann en låg risk för död (0,13%) och reoperation (3,0%) inom 90 dagar efter primär kirurgi, och likaså en låg risk för död (0,19%) och reoperation (6,2%) inom 90 dagar efter sekundär kirurgi. Inom 90 dagar efter primär kirurgi ökade dödsrisken bland patienter med högre ålder (särskilt vid över 60 års ålder) samt med samsjuklighet, och dödsrisken verkade minska bland de som opererades på sjukhus med hög operationsvolym. Reoperationsrisken inom 90 dagar efter primär och sekundär kirurgi ökade bland patienter med samsjuklighet. Patienter med högre ålder och mer samsjuklighet hade ökad risk för förlängd sjukhusvistelse efter både primär och sekundär kirurgi, och de som genomgick primär kirurgi på sjukhus med högre operationsvolym hade en minskad sådan risk.

8.2.3 Sammanfattning

Sammanfattningsvis är antirefluxkirurgi ett tryggt behandlingsalternativ för reflux. Denna kirurgi verkar minska risk för skivepitelcancer i svalg och struphuvud, samt för småcellig cancer och skivepitelcancer i lungan, och verkar även minska dödligheten bland patienter med reflux.

الملخص العلمي اليسير 8.3

تمهيد 8.3.1

يشكل الإرجاع المعدي المريئي (القلس) حالة مألوفة حيث يعاني حوالي 28% من البالغين في العالم الغربي وفي الشرق الأوسط، وحوالي 8% من البالغين في آسيا. ويتسبب القلس عن خلل وظيفي في البنية التشريحية النسيجية الواصلة بين المعدة والمريء، مما يسبب تسرب محتويات المعدة صعوداً إلى المريء مؤدياً الى الشعور بحرقة في المعدة والقلس

يعتبر القلس مرضاً حميداً، ولكنه قد يؤدي أحياناً الى مضاعفات مثل التهاب المريء، أو تغيرات نسيجية (مريء باريت) ونادراً مايؤدي الى سرطان المريء. تظهر بعض الدراسات ان القلس يمكن أن يؤدي إلى زيادة خطر الإصابة بسرطان الحنجرة، البلعوم، والرئه، والآلية المفترحة لزيادة هذا الخطر هي أن محتويات المعدة تؤثر على هذه الأعضاء عند صعودها الى أعلى من ارتفاع المريء

لمعالجة القلس تستخدم عادة مضادات الحموضة وخاصة مثبطات مضخة البروتون (م م ب) التي تقلل من حموضة محتويات المعدة، وتعتبر الجراحة المضادة للقلس خياراً آخر يهدف الى تصحيح الإختلال الوظيفي الذى أدى الى القلس

يتم إجراء الجراحة بلف جزء من المعدة حول الجزء السفلي من المريء، وبذا يقل الإرتجاع المعدي المريئي حيث تم احكام الفتحة العلوية للمعده. ليست هناك دراسات لاستقصاء ما إذا قللت الجراحة المضادة للقلس من خطر الإصابة بسرطان الحنجرة، البلعوم أو الرئه، وتقارن النشرة الحالية بين المعالجة الدوائية والجراحة المضادة للقلس من حيث الوفيات بين المرضى

طريقة البحث والنتائج 8.3.2

تعتمد الدراسات في هذه الأطروحة على سجلات مجموعة دول الشمال للجراحة المضادة للقلس، شاملة كافة المرضى البالغين الذين تم تشخيصهم كمرضى بالقلس أو تم تسجيلهم للجراحة المضادة للقلس في سجلات الدانمارك، فنلندا، ايسلندا النرويج والسويد خلال الأعوام 1980 – 2014. تتضمن هذه السجلات معلومات من السجلات الوطنية للسرطان وكذلك سجلات أسباب الوفيات

هدفت الدراسة الأولى والثانية إلى تقييم مدى الإقلال من خطر الإصابة بسرطان الحنجرة البلعوم أو الرئه في مرضى القلس مستخدمة سجلات مجموعة دول الشمال للجراحة المضادة للقلس. بالمقارنة مع مجموعة المقارنة فقد انخفضت في المرضى الذين خضعوا للجراحة نسبة خطر حدوث سرطان الحنجرة والبلعوم و سرطان الخلايا الصغيرة وسرطان الخلايا الحرشفية في الرئة ولكن ليس في السرطان الغدي للرئه. وازداد الإنخفاض مع مرور الوقت في سرطان الحنجرة. وعند المقارنة بين من عولجوا جراحيا ومن عولجوا دوائياً تبين عدم وجود فارق في نسبة الخطر في كل أنواع السرطان

هدفت الدراسة الثالثة معتمدة على سجلات مجموعة دول الشمال للجراحة المضادة للقلس إلى معرفة ما إذا كان للجراحة المضادة للقلس تأثير على الوفيات (على المدى الطويل) لكل الأسباب ولأسباب تتعلق بأمراض معينة، تم تقييم خطر الوفاة بين مرضى القلس الذين تمت معالجتهم دوائياً والذين عولجوا جراحياً. وأظهرت النتائج أن المعالجة الجراحية أدت الى أنخفاض معدل الوفيات بكل الأسباب، وبسبب أمراض القلب والأوعية وأمراض الجهاز التنفسي، وبسبب سرطان الحنجرة أو البلعوم ، وسرطان الرئة ، ولكن ليس في معدل الوفيات بسبب سرطان المريء

أما الدراسة الرابعة فقد هدفت إلى تقصي الخطر المطلق وعوامل الخطورة للوفاة ولإعادة إجراء الجراحة بسبب المضاعفات خلال 90 يوماً من الجراحة الأولية الجزء السفلي من المريء بالمنظار والجراحة الثانوية، بالإضافة إلى نسبة الخطر وعوامل الخطورة بسبب البقاء المطول في المستشفى بعد هذه العمليات الجراحية

شمل تقييم الجراحة الأولية بالمنظار المرضى الذين يعانون من القلس ممن خضعوا لأول عملية جراحية، وأولئك الذين خضعوا لجراحة ثانوية بما في ذلك من خضعوا سابقاً لعملية جراحية مضادة للقلس و خضعوا أيضاً لعملية ثانية

استندت هذه الدراسة إلى نسخة محدثة من سجلات مجموعة دول الشمال للجراحة المضادة للقلس ، بما في ذلك المرضى البالغين الذين خضعوا لجراحة مضادة للقلس بين العام 2000 إلى 2018 في الدول الشمال الخمس. أظهرت الدراسة انخفاض خطر الوفاة (0.13٪) وإعادة الجراحة (3.0٪) خلال 90 يومًا من الجراحة الأولية ، كذلك انخفاض خطر الوفاة وإعادة الجراحة (6.2٪) في غضون 90 يومًا من الجراحة الثانوية (0.19٪)

خلال 90 يوماً م الجراحة الأولية ازداد خطر الوفاة في المرضى كبار السن خاصة الذين تزيد أعمارهم عن 60 عاماً ولديهم أمراض مترافقة. ويبدو أن نسبة الخطر تدنت في المرضى الذين خضعوا للجراحة في مراكز متخصصة ذات كم كبير من الجراحات

كذلك ازداد خطر اعادة الجراحة خلال 90 يوماً تلت الجراحة الأولية والثانوية في المرضى ذوي الأمراض المترافقة وختاماً فان خطرإقامة المرضى كبار السن ذوو الأمراض المرافقة في المستشفى قد ازداد بعد الجراحة الأولية والثانوية وقد تدنى الخطر في المرضى الذين خضعوا للجراحة في المراكز المتخصصة ذات الكم الكبير من الجراحات

8.3.3 الخلاصة

نشكل الجراحة خياراً آمناً في معالجة القلس. ويبدو أن هذه الجراحة تقلل من خطر الإصابة بسرطان الحنجرة والبلعوم وسرطان الخلايا الصغيرة وسرطان الخلايا الحرشفية في الرئة ، وتقلل أيضاً من الوفيات في مرضى القلس

9 ACKNOWLEDGEMENTS

Jesper Lagergren, my main supervisor, you have been an immense source of inspiration from the moment I found UGIS' homepage and read your impressive CV in the spring of 2015. An incredibly efficient and prompt multitasker with clear devotion to work and family. Sympathetic. Supportive. Encouraging. Resourceful. Always pushing me forward and enabling my development. Do not underestimate my feelings of appreciation towards you.

Giola Santoni, my co-supervisor, the moment you stepped in to UGIS' offices, my research life became much easier. I never thought it possible that friendship could arise from code and datasets. I was wrong. It has been a pleasure to closely work with, and learn from you. Navigating through the hardships, pitfalls, and at times even drama, of NordASCo would not have been possible without your support.

John Maret-Ouda, my co-supervisor, I want to express my gratitude for your guidance since the beginning of my research journey, for your important role in making NordASCo possible, and for your sharp and clever contributions and inputs.

Eivind Ness-Jensen, my co-supervisor, thank you for your quick and meticulous feedback and suggestions on all my work.

Collaborators in the NordASCo project, **Eero Pukkala, Elsebeth Lynge, Joonas Kauppila, Laufey Tryggvadottir, Martti Färkkilä, My von Euler-Chelpin, Pål Romundstad.** Without your work with laying the foundation of NordASCo, this thesis would not have been possible to achieve. You have intellectually challenged me each step of the way and forced me to incessantly critique my work. Thank you for the academically enriching collaboration.

Current and former members of the research groups UGIS and SCS: Thank you all for creating a friendly atmosphere and motivating research environment. It has been a pleasure to work with each one of you. Special thanks to **Giulia Marras**, the office would not survive without you.

Special thanks to **Noor**, my lovely sister, for the beautiful illustrations in this thesis, to **Hsain**, for the support and guidance in moments of despair, to dear **Nabil**, for the timely translation of the summary to Arabic, and to my **Karolinska-brothers** for your wise inputs.

Dad, **Ziad**, thank you for providing me with the tools and conditions to thrive academically.

Mom, **Nahed**, thank you for your unconditional love and support in all my endeavors.

Rula, my beloved partner in life, you have been encouraging at every turn, supportive in every decision, and have consistently reminded me that anything is achievable. I am eternally grateful to you.

Finally, I want to thank **Karolinska Institutet** for the excellent academic and research environment.

10 REFERENCES

1. Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med. 1997;336(13):924-32.

2. Bredenoord AJ, Pandolfino JE, Smout AJ. Gastro-oesophageal reflux disease. Lancet. 2013;381(9881):1933-42.

3. Ness-Jensen E, Lagergren J. Tobacco smoking, alcohol consumption and gastro-oesophageal reflux disease. Best Pract Res Clin Gastroenterol. 2017;31(5):501-8.

4. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. Gut. 2012;61(10):1390-7.

5. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871-80.

6. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut. 2018;67(3):430-40.

7. Chatila AT, Nguyen MTT, Krill T, Roark R, Bilal M, Reep G. Natural history, pathophysiology and evaluation of gastroesophageal reflux disease. Dis Mon. 2019.

8. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal Reflux Disease: A Review. JAMA : the journal of the American Medical Association. 2020;324(24):2536-47.

9. Mohammed I, Cherkas LF, Riley SA, Spector TD, Trudgill NJ. Genetic influences in gastro-oesophageal reflux disease: a twin study. Gut. 2003;52(8):1085-9.

10. Cameron AJ, Lagergren J, Henriksson C, Nyren O, Locke GR, 3rd, Pedersen NL. Gastroesophageal reflux disease in monozygotic and dizygotic twins. Gastroenterology. 2002;122(1):55-9.

11. Andrici J, Cox MR, Eslick GD. Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2013;28(8):1258-73.

12. Ness-Jensen E, Hveem K, El-Serag H, Lagergren J. Lifestyle Intervention in Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol. 2016;14(2):175-82 e1-3.

13. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus G. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900-20; quiz 43.

14. Malfertheiner P, Nocon M, Vieth M, Stolte M, Jaspersen D, Koelz HR, et al. Evolution of gastro-oesophageal reflux disease over 5 years under routine medical care--the ProGERD study. Aliment Pharmacol Ther. 2012;35(1):154-64.

15. Armstrong D, Marshall JK, Chiba N, Enns R, Fallone CA, Fass R, et al. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults - update 2004. Can J Gastroenterol. 2005;19(1):15-35.

16. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997;112(6):1798-810.

17. Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev. 2007(2):CD003244.

18. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528-34.

19. Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol. 2006;4(12):1452-8.

20. Dean BB, Gano AD, Jr., Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol. 2004;2(8):656-64.

21. Weijenborg PW, Cremonini F, Smout AJ, Bredenoord AJ. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. Neurogastroenterol Motil. 2012;24(8):747-57, e350.

22. Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2013(5):CD002095.

23. Kahrilas PJ, Howden CW, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. Am J Gastroenterol. 2011;106(8):1419-25; quiz 26.

24. Kahrilas PJ, Jonsson A, Denison H, Wernersson B, Hughes N, Howden CW. Regurgitation is less responsive to acid suppression than heartburn in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2012;10(6):612-9.

25. Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology. 2001;120(7):1599-606.

26. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308-28; quiz 29.

27. Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. 2017;152(4):706-15.

28. Nugent CC, Terrell JM. H2 Blockers. StatPearls. Treasure Island (FL)2019.

29. Gutschow CA, Holscher AH. Surgical treatment of gastroesophageal reflux disease. Langenbecks Arch Surg. 2013;398(5):661-7.

30. Patti MG. An Evidence-Based Approach to the Treatment of Gastroesophageal Reflux Disease. JAMA Surg. 2016;151(1):73-8.

31. del Genio G, Tolone S, del Genio F, Rossetti G, Brusciano L, Pizza F, et al. Total fundoplication controls acid and nonacid reflux: evaluation by pre- and postoperative 24-h pH-multichannel intraluminal impedance. Surg Endosc. 2008;22(11):2518-23.

32. Ackroyd R, Watson DI, Majeed AW, Troy G, Treacy PJ, Stoddard CJ. Randomized clinical trial of laparoscopic versus open fundoplication for gastro-oesophageal reflux disease. Br J Surg. 2004;91(8):975-82.

33. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg. 2009;250(5):698-706.

34. Ljungdalh JS, Rubin KH, Durup J, Houlind KC. Trends of anti-reflux surgery in Denmark 2000-2017: a nationwide registry-based cohort study. Surg Endosc. 2020.

35. 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. Br J Surg. 2016;103(7):863-70.

36. Shan CX, Zhang W, Zheng XM, Jiang DZ, Liu S, Qiu M. Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. World J Gastroenterol. 2010;16(24):3063-71.

37. Broeders JA, Roks DJ, Ahmed Ali U, Watson DI, Baigrie RJ, Cao Z, et al. Laparoscopic anterior 180-degree versus nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. Ann Surg. 2013;257(5):850-9.

38. Broeders JA, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg. 2010;97(9):1318-30.

39. Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg. 2008;95(1):57-63.

40. Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. Br J Surg. 2008;95(12):1501-5.

41. Roks DJ, Koetje JH, Oor JE, Broeders JA, Nieuwenhuijs VB, Hazebroek EJ. Randomized clinical trial of 270 degrees posterior versus 180 degrees anterior partial laparoscopic fundoplication for gastro-oesophageal reflux disease. Br J Surg. 2017;104(7):843-51.

42. Hakanson BS, Lundell L, Bylund A, Thorell A. Comparison of Laparoscopic 270 degrees Posterior Partial Fundoplication vs Total Fundoplication for the Treatment of Gastroesophageal Reflux Disease: A Randomized Clinical Trial. JAMA Surg. 2019;154(6):479-86.

43. Memon MA, Subramanya MS, Hossain MB, Yunus RM, Khan S, Memon B. Laparoscopic anterior versus posterior fundoplication for gastro-esophageal reflux disease: a meta-analysis and systematic review. World J Surg. 2015;39(4):981-96.

44. Broeders JA, Roks DJ, Ahmed Ali U, Draaisma WA, Smout AJ, Hazebroek EJ. Laparoscopic anterior versus posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. Ann Surg. 2011;254(1):39-47.

45. Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C, Monami B, et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc. 2006;20(1):159-65.

46. Morgenthal CB, Shane MD, Stival A, Gletsu N, Milam G, Swafford V, et al. The durability of laparoscopic Nissen fundoplication: 11-year outcomes. J Gastrointest Surg. 2007;11(6):693-700.

47. Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J. Association Between Laparoscopic Antireflux Surgery and Recurrence of Gastroesophageal Reflux. JAMA : the journal of the American Medical Association. 2017;318(10):939-46.

48. Zhou T, Harnsberger C, Broderick R, Fuchs H, Talamini M, Jacobsen G, et al. Reoperation rates after laparoscopic fundoplication. Surg Endosc. 2015;29(3):510-4.

49. Ljungdalh JS, Rubin KH, Durup J, Houlind KC. Reoperation after antireflux surgery: a population-based cohort study. Br J Surg. 2020.

50. Maret-Ouda J, Lagergren J. The risk of mortality following secondary fundoplication in a population-based cohort study. Am J Surg. 2017;213(6):1160-2.

51. Niebisch S, Fleming FJ, Galey KM, Wilshire CL, Jones CE, Litle VR, et al. Perioperative risk of laparoscopic fundoplication: safer than previously reported-analysis of the American College of Surgeons National Surgical Quality Improvement Program 2005 to 2009. J Am Coll Surg. 2012;215(1):61-8; discussion 8-9.

52. Rantanen TK, Oksala NK, Oksala AK, Salo JA, Sihvo EI. Complications in antireflux surgery: national-based analysis of laparoscopic and open fundoplications. Arch Surg. 2008;143(4):359-65; discussion 65.

53. Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2010(3):CD003243.

54. Fiocca R, Mastracci L, Engstrom C, Attwood S, Ell C, Galmiche JP, et al. Long-term outcome of microscopic esophagitis in chronic GERD patients treated with esomeprazole or laparoscopic antireflux surgery in the LOTUS trial. Am J Gastroenterol. 2010;105(5):1015-23.

55. Garg SK, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2015(11):CD003243.

56. Maret-Ouda J, Brusselaers N, Lagergren J. What is the most effective treatment for severe gastro-oesophageal reflux disease? BMJ (Clinical research ed). 2015;350:h3169.

57. Tran T, Spechler SJ, Richardson P, El-Serag HB. Fundoplication and the risk of esophageal cancer in gastroesophageal reflux disease: a Veterans Affairs cohort study. Am J Gastroenterol. 2005;100(5):1002-8.

58. Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. JAMA : the journal of the American Medical Association. 2001;285(18):2331-8.

59. Jaspersen D, Kulig M, Labenz J, Leodolter A, Lind T, Meyer-Sabellek W, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. Aliment Pharmacol Ther. 2003;17(12):1515-20.

60. Ghisa M, Della Coletta M, Barbuscio I, Marabotto E, Barberio B, Frazzoni M, et al. Updates in the field of non-esophageal gastroesophageal reflux disorder. Expert Rev Gastroenterol Hepatol. 2019;13(9):827-38.

61. Harnik IG. In the Clinic. Gastroesophageal Reflux Disease. Ann Intern Med. 2015;163(1):ITC1.

62. Pacheco A, Domingo C. Airway reflux: an emerging topic in respiratory medicine. Lancet Respir Med. 2018;6(11):810-2.

63. Asaoka D, Nagahara A, Matsumoto K, Hojo M, Watanabe S. Current perspectives on reflux laryngitis. Clin J Gastroenterol. 2014;7(6):471-5.

64. Sasaki CT, Doukas SG, Costa J, Vageli DP. Biliary reflux as a causal factor in hypopharyngeal carcinoma: New clinical evidence and implications. Cancer. 2019;125(20):3554-65.

65. Johnston N, Ondrey F, Rosen R, Hurley BP, Gould J, Allen J, et al. Airway reflux. Ann N Y Acad Sci. 2016;1381(1):5-13.

66. Johnston N, Bulmer D, Gill GA, Panetti M, Ross PE, Pearson JP, et al. Cell biology of laryngeal epithelial defenses in health and disease: further studies. Ann Otol Rhinol Laryngol. 2003;112(6):481-91.

67. Johnston N, Wells CW, Samuels TL, Blumin JH. Pepsin in nonacidic refluxate can damage hypopharyngeal epithelial cells. Ann Otol Rhinol Laryngol. 2009;118(9):677-85.

68. Broers C, Tack J, Pauwels A. Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. Aliment Pharmacol Ther. 2018;47(2):176-91.

69. Hayes D, Jr. A review of bronchiolitis obliterans syndrome and therapeutic strategies. J Cardiothorac Surg. 2011;6:92.

70. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev. 2011(1):CD004823.

71. Ford C. Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope. 2006;116(9):1717-8; author reply 8.

72. Kiljander TO, Junghard O, Beckman O, Lind T. Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2010;181(10):1042-8.

73. Tutuian R, Vela MF, Hill EG, Mainie I, Agrawal A, Castell DO. Characteristics of symptomatic reflux episodes on Acid suppressive therapy. Am J Gastroenterol. 2008;103(5):1090-6.

74. Iqbal M, Batch AJ, Spychal RT, Cooper BT. Outcome of surgical fundoplication for extraesophageal (atypical) manifestations of gastroesophageal reflux disease in adults: a systematic review. J Laparoendosc Adv Surg Tech A. 2008;18(6):789-96.

75. Francis DO, Goutte M, Slaughter JC, Garrett CG, Hagaman D, Holzman MD, et al. Traditional reflux parameters and not impedance monitoring predict outcome after fundoplication in extraesophageal reflux. Laryngoscope. 2011;121(9):1902-9.

76. Lechien JR, Dapri G, Dequanter D, Rodriguez Ruiz A, Marechal MT, De Marrez LG, et al. Surgical Treatment for Laryngopharyngeal Reflux Disease: A Systematic Review. JAMA Otolaryngol Head Neck Surg. 2019;145(7):655-66.

77. Perrin-Fayolle M, Gormand F, Braillon G, Lombard-Platet R, Vignal J, Azzar D, et al. Long-term results of surgical treatment for gastroesophageal reflux in asthmatic patients. Chest. 1989;96(1):40-5.

78. Sontag SJ, O'Connell S, Khandelwal S, Greenlee H, Schnell T, Nemchausky B, et al. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. Am J Gastroenterol. 2003;98(5):987-99.

79. Silva AP, Tercioti-Junior V, Lopes LR, Coelho-Neto Jde S, Bertanha L, Rodrigues PR, et al. Laparoscopic antireflux surgery in patients with extra esophageal symptoms related to asthma. Arq Bras Cir Dig. 2014;27(2):92-5.

80. Chen D, Wang Z, Hu Z, Liang Y, Xiao F, Wu J. Typical symptoms and not positive reflux-cough correlation predict cure of gastroesophageal reflux disease related chronic cough after laparoscopic fundoplication: a retrospective study. BMC Gastroenterol. 2019;19(1):108.

81. Lugaresi M, Aramini B, Daddi N, Baldi F, Mattioli S. Effectiveness of antireflux surgery for the cure of chronic cough associated with gastroesophageal reflux disease. World J Surg. 2015;39(1):208-15.

82. Biswas Roy S, Elnahas S, Serrone R, Haworth C, Olson MT, Kang P, et al. Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease. J Thorac Cardiovasc Surg. 2018;155(6):2762-71 e1.

83. Hartwig MG, Anderson DJ, Onaitis MW, Reddy S, Snyder LD, Lin SS, et al. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. Ann Thorac Surg. 2011;92(2):462-8; discussion; 8-9.

84. Hoppo T, Jarido V, Pennathur A, Morrell M, Crespo M, Shigemura N, et al. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. Arch Surg. 2011;146(9):1041-7.

85. Sidhwa F, Moore A, Alligood E, Fisichella PM. Diagnosis and Treatment of the Extraesophageal Manifestations of Gastroesophageal Reflux Disease. Ann Surg. 2017;265(1):63-7.

86. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. CA Cancer J Clin. 2013;63(4):232-48.

87. Maret-Ouda J, Santoni G, Wahlin K, Artama M, Brusselaers N, Farkkila M, et al. Esophageal Adenocarcinoma After Antireflux Surgery in a Cohort Study From the 5 Nordic Countries. Ann Surg. 2019.

88. El-Serag HB, Hepworth EJ, Lee P, Sonnenberg A. Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. Am J Gastroenterol. 2001;96(7):2013-8.

89. Lagergren J, Lindam A. Increased risk of laryngeal and pharyngeal cancer after gastrectomy for ulcer disease in a population-based cohort study. Br J Cancer. 2012;106(7):1342-5.

90. Zhang D, Zhou J, Chen B, Zhou L, Tao L. Gastroesophageal reflux and carcinoma of larynx or pharynx: a meta-analysis. Acta Otolaryngol. 2014;134(10):982-9.

91. Kuo CL, Chen YT, Shiao AS, Lien CF, Wang SJ. Acid reflux and head and neck cancer risk: A nationwide registry over 13 years. Auris Nasus Larynx. 2015;42(5):401-5.

92. Langevin SM, Michaud DS, Marsit CJ, Nelson HH, Birnbaum AE, Eliot M, et al. Gastric reflux is an independent risk factor for laryngopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2013;22(6):1061-8.

93. Parsel SM, Wu EL, Riley CA, McCoul ED. Gastroesophageal and Laryngopharyngeal Reflux Associated With Laryngeal Malignancy: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;17(7):1253-64 e5.

94. Kim SY, Park B, Lim H, Kim M, Kong IG, Choi HG. Increased risk of larynx cancer in patients with gastroesophageal reflux disease from a national sample cohort. Clin Otolaryngol. 2019;44(4):534-40.

95. Bacciu A, Mercante G, Ingegnoli A, Ferri T, Muzzetto P, Leandro G, et al. Effects of gastroesophageal reflux disease in laryngeal carcinoma. Clin Otolaryngol Allied Sci. 2004;29(5):545-8.

96. Vaezi MF, Qadeer MA, Lopez R, Colabianchi N. Laryngeal cancer and gastroesophageal reflux disease: a case-control study. Am J Med. 2006;119(9):768-76.

97. Qadeer MA, Colabianchi N, Vaezi MF. Is GERD a risk factor for laryngeal cancer? Laryngoscope. 2005;115(3):486-91.

98. Parsel SM, Iarocci AL, Gastanaduy M, Winters RD, Marino JP, McCoul ED. Reflux Disease and Laryngeal Neoplasia in Nonsmokers and Nondrinkers. Otolaryngol Head Neck Surg. 2020;163(3):560-2.

99. Agrawal K, Markert RJ, Agrawal S. Risk factors for adenocarcinoma and squamous cell carcinoma of the esophagus and lung. AME Medical Journal. 2018;3(3).

100. Vereczkei A, Horvath OP, Varga G, Molnar TF. Gastroesophageal reflux disease and non-small cell lung cancer. Results of a pilot study. Dis Esophagus. 2008;21(5):457-60.

101. Choi WI, Jeong J, Lee CW. Association between EGFR mutation and ageing, history of pneumonia and gastroesophageal reflux disease among patients with advanced lung cancer. Eur J Cancer. 2019;122:101-8.

102. Dresler H, Keizman D, Mamtani R, Gottfried M, Maimon N, Mishaeli M, et al. The association between proton pump inhibitors (PPI) use for gastroesophageal reflux disease (GERD) and lung cancer (LC): A nested case-control study. J Clin Oncol. 2017;35.

103. Hsu CK, Lai CC, Wang K, Chen L. Risk of lung cancer in patients with gastro-esophageal reflux disease: a population-based cohort study. PeerJ. 2016;4:e2753.

104. Eells AC, Mackintosh C, Marks L, Marino MJ. Gastroesophageal reflux disease and head and neck cancers: A systematic review and meta-analysis. Am J Otolaryngol. 2020;41(6):102653.

105. Steuer CE, El-Deiry M, Parks JR, Higgins KA, Saba NF. An update on larynx cancer. CA Cancer J Clin. 2017;67(1):31-50.

106. Dutta R, Husain Q, Kam D, Dubal PM, Baredes S, Eloy JA. Laryngeal Papillary Squamous Cell Carcinoma: A Population-Based Analysis of Incidence and Survival. Otolaryngol Head Neck Surg. 2015;153(1):54-9.

107. Chow LQM. Head and Neck Cancer. N Engl J Med. 2020;382(1):60-72.

108. Bosetti C, Gallus S, Franceschi S, Levi F, Bertuzzi M, Negri E, et al. Cancer of the larynx in non-smoking alcohol drinkers and in non-drinking tobacco smokers. Br J Cancer. 2002;87(5):516-8.

109. Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M, et al. Red meat and cancer risk in a network of case-control studies focusing on cooking practices. Ann Oncol. 2013;24(12):3107-12.

110. Paget-Bailly S, Cyr D, Luce D. Occupational exposures and cancer of the larynx-systematic review and meta-analysis. J Occup Environ Med. 2012;54(1):71-84.

111. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin. 2017;67(1):51-64.

112. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet. 2019;394(10192):64-80.

113. Wycliffe ND, Grover RS, Kim PD, Simental A, Jr. Hypopharyngeal cancer. Top Magn Reson Imaging. 2007;18(4):243-58.

114. Clump DA, Bauman JE, Ferris RL. Cancer of the oropharynx. Surg Oncol Clin N Am. 2015;24(3):509-20.

115. Huber MA, Tantiwongkosi B. Oral and oropharyngeal cancer. Med Clin North Am. 2014;98(6):1299-321.

116. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92.

117. Ansary-Moghaddam A, Huxley RR, Lam TH, Woodward M. The risk of upper aero digestive tract cancer associated with smoking, with and without concurrent alcohol consumption. Mt Sinai J Med. 2009;76(4):392-403.

118. Lu Y, Sobue T, Kitamura T, Matsuse R, Kitamura Y, Matsuo K, et al. Cigarette smoking, alcohol drinking, and oral cavity and pharyngeal cancer in the Japanese: a population-based cohort study in Japan. Eur J Cancer Prev. 2018;27(2):171-9.

119. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.

120. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018;553(7689):446-54.

121. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 2017;17(12):725-37.

122. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, et al. Non-small-cell lung cancer. Nat Rev Dis Primers. 2015;1:15009.

123. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced NonSmall-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019;37(28):2518-27.

124. Kalemkerian GP, Schneider BJ. Advances in Small Cell Lung Cancer. Hematol Oncol Clin North Am. 2017;31(1):143-56.

125. Mao Y, Yang D, He J, Krasna MJ. Epidemiology of Lung Cancer. Surg Oncol Clin N Am. 2016;25(3):439-45.

126. Durham AL, Adcock IM. The relationship between COPD and lung cancer. Lung Cancer. 2015;90(2):121-7.

127. Qu YL, Liu J, Zhang LX, Wu CM, Chu AJ, Wen BL, et al. Asthma and the risk of lung cancer: a meta-analysis. Oncotarget. 2017;8(7):11614-20.

128. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med. 2000;161(1):5-8.

129. Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol. 2006;24(28):4539-44.

130. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.

131. Committee NM-S. NOMESCO Classification of Surgical Procedures (NCSP), version 1.16. Nordic Medico-Statistical Committee (NOMESCO). 2011.

132. Anell A. The public-private pendulum--patient choice and equity in Sweden. N Engl J Med. 2015;372(1):1-4.

133. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. Scand J Public Health. 2017;45(17_suppl):14-9.

134. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11:450.

135. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health. 2012;40(6):505-15.

136. Pukkala E, Engholm G, Hojsgaard Schmidt LK, Storm H, Khan S, Lambe M, et al. Nordic Cancer Registries - an overview of their procedures and data comparability. Acta Oncol. 2018;57(4):440-55.

137. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765-73.

138. Johansson LA, Bjorkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995. J Clin Epidemiol. 2009;62(11):1202-9.

139. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.

140. Erlangsen A, Fedyszyn I. Danish nationwide registers for public health and health-related research. Scand J Public Health. 2015;43(4):333-9.

141. National Board of Health and Welfare. Swedish Prescribed Drug Register. 2020 [Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-prescribed-drug-register/] Accessed February 02, 2021.

142. Maret-Ouda J, Wahlin K, Artama M, Brusselaers N, Farkkila M, Lynge E, et al. Cohort profile: the Nordic Antireflux Surgery Cohort (NordASCo). BMJ Open. 2017;7(6):e016505.

143. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. Surg Oncol Clin N Am. 2015;24(3):379-96.

144. Tramacere I, La Vecchia C, Negri E. Tobacco smoking and esophageal and gastric cardia adenocarcinoma: a meta-analysis. Epidemiology. 2011;22(3):344-9.

145. Riley CA, Marino MJ, Hawkey N, Lawlor CM, McCoul ED. Sinonasal Tract Inflammation as a Precursor to Nasopharyngeal Carcinoma: A Systematic Review and Meta-Analysis. Otolaryngol Head Neck Surg. 2016;154(5):810-6.

146. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825-31.

147. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 2010;32(10):1222-7.

148. Annese V, Beaugerie L, Egan L, Biancone L, Bolling C, Brandts C, et al. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. J Crohns Colitis. 2015;9(11):945-65.

149. Luedde T, Schwabe RF. NF-kappaB in the liver--linking injury, fibrosis and hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2011;8(2):108-18.

150. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 2011;32(4):605-44.

151. Bhatt SP, Kim YI, Harrington KF, Hokanson JE, Lutz SM, Cho MH, et al. Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years. Thorax. 2018;73(5):414-21.

152. Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. J Hepatol. 2018;69(3):718-35.

153. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PLoS One. 2018;13(3):e0194127.

154. Hsu WT, Lai CC, Wang YH, Tseng PH, Wang K, Wang CY, et al. Risk of pneumonia in patients with gastroesophageal reflux disease: A population-based cohort study. PLoS One. 2017;12(8):e0183808.

155. Linz D, Hohl M, Vollmar J, Ukena C, Mahfoud F, Bohm M. Atrial fibrillation and gastroesophageal reflux disease: the cardiogastric interaction. Europace. 2017;19(1):16-20.

11 SUPPLEMENTARY DOCUMENTS

Supplementary Table 1. *Codes defining participants with gastroesophageal reflux disease (GERD), severe GERD (reflux esophagitis or Barrett's esophagus) and antireflux surgery*

	Sweden	Finland	Denmark	Iceland	Norway
GERD					
GERD	ICD-10: K21.9	ICD-10: K21.9	ICD-10: K21.9	ICD-10: K21.9	ICD-10: K21.9
Hiatal hernia	ICD-7: 560.40 ICD-8: 551.30 ICD-9: 553D ICD-10: K44	ICD-7: 560.40 ICD-8: 551.30 ICD-9: 5513A ICD-10: K44	ICD-8: 551.30, 551.39 ICD-7: DK44	ICD-10: K44	ICD-10: K44
Heartburn	ICD-7: 784.30 ICD-8: 784.30 ICD-9: 787B ICD-10: R12	ICD-7: 784.30 ICD-8: 784.30 ICD-9: 7871A ICD-10: R12	ICD-8: 784.39 ICD-10: DR12	ICD-10: R12	ICD-10: R12
Esophagitis	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 530B, 530C ICD-10: K21.0, K20	ICD-7: 539.11, 539.12; ICD-8: 530.93, 530.94; ICD-9: 5301A, 5301C-D, 5301X ICD-10: K21.0, K20	ICD-8: 530.90 ICD-10: DK21.0, DK20	ICD-10: K21.0, K20	ICD-10: K21.0, K20
Barrett's esophagus	ICD-10: K22.7	ICD-9: 5301B ICD-10: K22.7	ICD-10: DK22.7	ICD-10: 22.7	ICD-10: K22.7
Severe GERD					
Reflux esophagitis	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 530B, 530C ICD-10: K21.0	ICD-7: 539.11, 539.12; ICD-8: 530.93, 530.94; ICD-9: 5301A, 5301C-D, 5301X; ICD-10: K21.0	ICD-8: 530.90 ICD-10: DK21.0	ICD-10: K21.0	ICD-10: K21.0
Barrett's esophagus	ICD-10: K22.7	ICD-9: 5301B ICD-10: K22.7	ICD-10: DK22.7	ICD-10: 22.7	ICD-10: K22.7
Antireflux surgery					
Historical codes prior to 1997	4272	6241, 6242, 6249, 6251, 6259	4054, 4056, 4074, 4076, 4080, 4084		
Antireflux surgery	JBC00, JBC01	JBC00, JBC01	KJBC00, KJBC01	JBC00, JBC01	JBC00, JBC01
Other surgeries of the diaphragm and due to GERD	JBW96, JBW97	JBW96, JBW97	KJBW96, KJBW97	JBW96, JBW97	JBW96, JBW97