

## Title

Survival after antireflux surgery versus medication in patients with reflux oesophagitis or Barrett's oesophagus: a multinational cohort study

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### **Author's contribution**

Study concept and design were done by all authors. Acquisition of data was done by all authors.

Analysis and interpretation of data were done by M.Y., G.S., and J.L. Drafting of the manuscript

was done by M.Y. and J.L. Critical revision of the manuscript for important intellectual content

was done by all authors. Statistical analysis was done by M.Y. and G.S. Funding was obtained by

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None.

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## Abstract

**Background:** To examine the hypothesis that antireflux surgery with fundoplication improves long-term survival compared to antireflux medication in patients with reflux oesophagitis or Barrett's oesophagus.

**Method:** Individuals aged between 18 and 70 years with reflux oesophagitis or Barrett's oesophagus (intestinal metaplasia) documented from in-hospital and specialized out-patient care were selected from national patient registries in Denmark, Finland, Iceland, or Sweden from 1980 through 2014. The study investigated all-cause mortality and disease-specific mortality, comparing patients who had undergone open or laparoscopic antireflux surgery with fundoplication with those using antireflux medication. Multivariable Cox regression analysis was performed to estimate hazard ratios (HR) with 95% confidence intervals (CI) of all-cause mortality and disease-specific mortality, adjusted for sex, age, calendar period, country, and comorbidity.

**Results:** Some 240,226 patients with reflux oesophagitis or Barrett's oesophagus were included of whom 33,904 (14.1%) underwent antireflux surgery. The risk of all-cause mortality was lower after antireflux surgery compared to medication (HR 0.61, 95% CI 0.58-0.63), and lower after laparoscopic (HR 0.56, 95% CI 0.52-0.60) than open surgery (HR 0.80, 95% CI 0.70-0.91). After antireflux surgery, mortality was decreased 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 oesophageal cancer (HR 1.05, 95% CI 0.87-1.28). The decreased mortality rates generally remained over time.

**Conclusions:** In patients with reflux oesophagitis or Barrett's oesophagus, antireflux surgery is associated with a lower mortality from all causes, cardiovascular disease, respiratory disease, laryngeal or pharyngeal cancer, and lung cancer, but not from oesophageal cancer, compared to antireflux medication.

## Introduction

Gastro-oesophageal reflux disease (GORD) affects 9-28% of adults in the Western world and the Middle East, and 3-8% of adults in East Asia.(1) Risk factors are heredity, obesity, and tobacco smoking.(2) GORD is associated with an increased risk of adenocarcinoma of the oesophagus, cancer of the larynx and pharynx, and possibly cancer of the lung, which all have a poor prognosis.(3-7) GORD might also increase the risk of cardiovascular diseases respiratory diseases including atrial fibrillation, idiopathic pulmonary fibrosis, pneumonia, asthma, and chronic obstructive pulmonary disease.(8-11) This indicates that GORD might reduce life expectancy.

GORD is predominantly treated with a proton pump inhibitor, which decreases the acidity of the gastric contents, and thus usually relieves GORD-symptoms and heals reflux oesophagitis.(12) However, proton pump inhibitors do not stop non-acidic reflux or regurgitation.(13) In contrast, antireflux surgery with fundoplication creates a barrier to both acidic and non-acidic reflux. This may lower the risk for mortality compared to patients who receive antireflux medication. There are only few studies addressing this association and most included a small number of patients and had insufficient length or completeness of follow-up. Most of these studies have assessed open rather than laparoscopic antireflux surgery, which has replaced the open approach.(14-16) In this multi-national cohort study with complete and long term follow up it was hypothesized that antireflux surgery is associated with better survival compared to antireflux medication in patients with reflux oesophagitis or Barrett's oesophagus.

## Methods

### Design

This population-based cohort study included all individuals aged between 18 and 70 years with reflux oesophagitis or Barrett's oesophagus (intestinal metaplasia) documented from in-hospital and specialized out-patient care in any of the national patient registries in Denmark, Finland, Iceland, or Sweden, from 1980 through 2014. The study investigated all-cause mortality and disease-specific mortality, comparing patients who had undergone antireflux surgery with fundoplication with those using antireflux medication. Ethical and data permissions were retrieved from all relevant authorities within each country, as described in detail elsewhere.(17)

### Cohort

Data were retrieved from well-established and nationwide health data registries in the four countries, i.e. patient registries, cancer registries, and mortality registries. The diagnosis of reflux oesophagitis or Barrett's oesophagus was documented from in-hospital and specialized out-patient care in all national patient registries following confirmation by endoscopy and histology. Complete nationwide coverage of the patient registries was reached in the 1970s (Finland), 1978 (Denmark), 1987 (Sweden), and 1999 (Iceland). The similarity in structure of the Nordic countries' health data registries, combined with the system of personal identity codes of each resident in these countries, allowed linkages of individuals' data between the registries.(17, 18) The overall study period was from January 1, 1980 to December 31, 2014, but with different start and end years depending on the country. Individuals with a cancer of the

oesophagus, larynx, pharynx, or lung before the diagnosis of reflux oesophagitis or Barrett's oesophagus were excluded.

## **Exposures**

Antireflux surgery with open or laparoscopic fundoplication was compared with antireflux medication, mainly a proton pump inhibitor (or occasionally a histamine-2 receptor antagonist). The codes defining reflux oesophagitis, Barrett's oesophagus, and fundoplication in the patient registries are shown in Supplementary Table 1. The diagnoses and surgical procedures in the Nordic patient registries have high validity with positive predictive values close to 100%(19-21). The recording of the diagnoses reflux oesophagitis and Barrett's oesophagus in these registries requires detection by endoscopy and confirmation by histology. Because data on medication were not available, the use of antireflux medication (proton pump inhibitors or histamine-2-receptor antagonists) recorded in the Swedish Prescribed Drug Registry was confirmed in a validation sample of 7,339 Swedish non-operated participants with reflux oesophagitis or Barrett's oesophagus. 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 the data of diagnosis, which suggests a low use of antireflux medication for other indications than GORD. The slight frequency (2.7%) of non-use of antireflux medication is probably explained by over-the-counter purchase and under-reporting to the Drug Registry.

## **Outcomes**

The main outcome was all-cause mortality. Secondary outcomes were disease-specific mortality from: 1) cardiovascular disease, 2) respiratory disease, 3) oesophageal cancer, 4) laryngeal or pharyngeal cancer, and 5) lung cancer. All outcomes were identified in the cause of death registries by using the relevant diagnosis codes (Supplementary Table 2). The Nordic cause of death registries have virtually 100% completeness and accuracy for all-cause mortality, and at least 96% completeness and accuracy for specific causes of death.(22-24)

### **Statistical analysis**

The data management and statistical analyses followed a pre-defined study protocol and were conducted using IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY, USA). The follow-up of the patients in the cohort started from the date of the first diagnosis of reflux oesophagitis or Barrett's oesophagus. Patients who underwent antireflux surgery were censored from the non-operated group at the date of admission for surgery and were included in the antireflux surgery group from the date of surgery. Survival after antireflux surgery was compared to survival after antireflux medication (reference) by means of Kaplan-Meier survival plot and crude log-rank statistic. Multivariable Cox regression was used to compute hazard ratios (HR) with 95% confidence intervals (CIs) of mortality between the surgery group and the medication group. The HRs were adjusted for five potential confounders: 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  $\geq 2$ ). Comorbidity was assessed using the most recent version of the well-validated Charlson Comorbidity Index, which is a comorbidity score system mainly developed for the

assessment of survival after interventions.(25) The Charlson Comorbidity Index included diagnoses recorded in the patient registries up to 1 year before the diagnosis of reflux oesophagitis or Barrett's oesophagus. This restriction in time was made to include all relevant comorbidities but avoid including comorbidities or complications caused by reflux oesophagitis or Barrett's oesophagus or their treatment. Overall HRs for mortality were calculated both for the entire follow-up time (0-34 years), and for each of four pre-defined follow-up categories after reflux oesophagitis or Barrett's oesophagus diagnosis or antireflux surgery: 0-5, >5-10, >10-15, and >15 years. The analyses of the main outcome (all-cause mortality) were also stratified by sex, age, comorbidity, and surgical approach (open or laparoscopic fundoplication). Data on surgical approach were available from the year 1996 onwards, which restricted these particular analyses to a sub-cohort of patients during the period from 1996 through 2014. The proportionality hazards assumption was verified using Schoenfeld residuals. Finally, the absolute risks of post-operative all-cause mortality within 30 and 90 days of surgery were calculated for all antireflux surgery in the total cohort, and separately for open and laparoscopic antireflux surgery in the sub-cohort of patients 1996-2014.

## Results

### Participants

The cohort included 240,226 patients with reflux oesophagitis or Barrett's oesophagus. Of these, 33,904 (14.1%) underwent antireflux surgery and 206,322 (85.9%) used antireflux medication. The number of person-years at risk were 445,594 after antireflux surgery and 1,851,087 after antireflux medication. The surgery group was younger and had less comorbidity compared to the medication group (Table 1).

### All-cause mortality

Mortality from any cause was observed in 4,496 (13.3%) participants in the antireflux surgery group and in 39,390 (19.1%) participants in the antireflux medication group. As illustrated in Figure 1, the Kaplan-Meier survival plot showed a better survival in the antireflux surgery group compared to the antireflux medication group ( $p < 0.0001$ ). The adjusted risk of overall all-cause mortality was decreased after antireflux surgery compared to antireflux medication (HR 0.61, 95% CI 0.58-0.63). Mortality remained lower within each follow-up period but slightly attenuated over time (Table 2). The reduction in adjusted risk of all-cause mortality was similar between the sexes and age groups, but was more pronounced among participants with comorbidity (HR 0.47 [95% CI 0.37-0.58] for Charlson Comorbidity Index score  $\geq 2$ ), than those without (HR 0.62 [95% CI 0.59-0.64] for Charlson Comorbidity Index score 0).

Defined by surgical approach, the adjusted risk of all-cause mortality was lower after laparoscopic fundoplication (HR 0.56, 95% CI 0.52-0.60) than after open fundoplication (HR

0.80, 95% CI 0.70-0.91). This pattern remained in analyses categorized by follow-up period, sex, age, and comorbidity (Table 3). Compared to antireflux medication, laparoscopic fundoplication was followed by a gradually decreasing risk of mortality among those with higher Charlson Comorbidity Index scores (from HR 0.61 [95% CI 0.56-0.67] with a score of 0 to HR 0.25 [95% CI 0.15-0.40] with a score of  $\geq 2$ ).

### **Disease-specific mortality**

Compared to antireflux medication, antireflux surgery was associated with a decreased adjusted risk of 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) (Table 4). Mortality remained lower in each follow-up period and was even lower for laryngeal or pharyngeal cancer after >15 years of follow-up (HR 0.18, 95% CI 0.04-0.81). No reduction in the risk of mortality from oesophageal cancer was found after antireflux surgery compared to antireflux medication (overall HR 1.05 [95% CI 0.87-1.28] and HR 1.09 [95% CI 0.74-1.60] after >15 years of follow-up).

### **Short-term mortality after antireflux surgery**

The all-cause mortality rates within 30 days and 90 days of antireflux surgery were 0.09% (n=32) and 0.20% (n=67), respectively. The rates were 0.05% (n=10) within 30 days and 0.09% (n=20) within 90 days of laparoscopic surgery, and 0.13% (n=3) within 30 days and 0.39% (n=9) within 90 days of open surgery. The mortality rate difference between laparoscopic and open

fundoplication was 0.08% (95% CI -0.01%-0.33%) within 30 days, and 0.29% (95% CI 0.10%-0.64%) within 90 days of surgery.

## Discussion

This study found that patients with reflux oesophagitis or Barrett's oesophagus who underwent antireflux surgery with fundoplication have a lower all-cause mortality compared to patients using antireflux medication. Mortality from cardiovascular disease, respiratory disease, laryngeal or pharyngeal cancer, and lung cancer, but not for oesophageal cancer, was also lower for patients after surgery. All-cause mortality was lower after laparoscopic than open fundoplication.

Strengths of this study are the population-based design, large sample size, and the complete and long follow-up. The inclusion of patients with objectively determined reflux oesophagitis or Barrett's oesophagus only, counteracted both misclassification of GORD and biased selection of patients with milder GORD in the non-surgical group. The adjustment for known prognostic factors should reduce confounding, but a weakness is that residual or unmeasured confounding cannot be ruled out. A particularly relevant issue is possible biased selection of individuals for surgery who are more healthy and fit, have less comorbidity, obesity, and are not heavy users of tobacco or alcohol. However, comorbidity was adjusted for. Obesity, tobacco smoking, and heavy alcohol consumption were indirectly adjusted for by their close association with diseases included in the Charlson Comorbidity Index, i.e. diabetes mellitus type 2, chronic obstructive pulmonary disease, and liver disease.(26-28) It should also be noted that all-cause mortality was decreased also when the analyses were restricted to participants with a Charlson Comorbidity Index score of 0. To further assess potential bias from selection or confounding, the risk of colon cancer was assessed in the antireflux surgery group compared to the antireflux

medication group with reflux oesophagitis or Barrett's oesophagus. Colon cancer was chosen because it is unrelated to GORD and its treatment. Also colon cancer is well registered ( completeness and accuracy) in the cancer registries and occurs frequently in both sexes with high incidence in the Nordic countries.(29) The results showed no decreased risk of colon cancer in the antireflux surgery group compared to antireflux medication group (HR 1.16, 95% CI 1.01-1.33), which further argues against a strong influence of confounding due to selection of more fit and healthy patients for antireflux surgery. Another limitation is recurrence of GORD after antireflux surgery. This is not uncommon and occurred in 17.7% after laparoscopic fundoplication in a recent population-based study from Sweden.(30) This exposure misclassification of recurrence of GORD should not explain or contribute to the associations found, but rather attenuate the reported risk estimates. Recurrence of GORD could therefore explain the tendency that many risk estimates attenuated with longer follow-up after surgery. One of the limitations is also the unavailability of data on antireflux medication use in all non-operated cohort participants. However, the validation study in a large sample of the present cohort showed that almost all non-operated patients with reflux oesophagitis or Barrett's oesophagus used antireflux medication, which is in agreement with best practice guidelines.(31) Data on specific surgical codes of antireflux surgery techniques were not available, but the main techniques in the Nordic countries are laparoscopic Nissen (360 degree wrap) and Toupet (270 posterior wrap), which have similar effects on GORD.(32) Nordic countries have similar prevalence of reflux oesophagitis, Barrett's oesophagus, and GORD in general compared to other Western countries,(1, 33) which suggests that the findings of the present study could be generalised to Western populations.

Few studies have attempted to assess whether antireflux surgery influences survival in patients with GORD. Similar to the results of the present study, a study from the United States found lower cumulative mortality rate in patients who had undergone antireflux surgery (37% [n=946]) compared to age-matched patients using antireflux medication for GORD (47% [n=1892]) ( $p < 0.0001$ ).<sup>(15)</sup> Conversely, a randomized clinical trial from the United States showed increased all-cause mortality (relative risk 1.57, 95% CI 1.01-2.46) after antireflux surgery (n=82) compared to antireflux medication (n=146), mainly due to increased deaths from cardiovascular disease in the surgery group.<sup>(14)</sup> Compared to these previous studies, the present study had longer follow-up and larger sample size and only included patients with objectively confirmed severe GORD, i.e. reflux oesophagitis or Barrett's oesophagus.

A possible biological mechanism for the finding indicating better survival after antireflux surgery than after antireflux medication could be the one hypothesized, i.e. antireflux surgery hinders both acidic and non-acidic reflux and counteracts extra-oesophageal diseases associated with severe GORD that might affect survival, e.g. atrial fibrillation, idiopathic pulmonary fibrosis, pneumonia, asthma, and chronic obstructive pulmonary disease.<sup>(8-11)</sup>

Laparoscopic fundoplication has been the primary procedure over open fundoplication from the 1990s onwards, and these approaches are similarly effective in the treatment of GORD.<sup>(34, 35)</sup> Patients with more advanced GORD or presence of abdominal adhesions following previous surgical interventions could render antireflux surgery technically more difficult. These patients

may be more likely to be selected for open surgery, which could explain the more pronounced decreased mortality in GORD patients who underwent laparoscopic compared to open fundoplication. Another explanation could be stricter criteria for eligibility or consideration of antireflux surgery during a more recent calendar period, although calendar period was adjusted for in the analyses.

Studies have yielded conflicting results regarding the influence of antireflux surgery on the risk of developing oesophageal adenocarcinoma.(36, 37) A recent large Nordic cohort study found no reduction in incidence after antireflux surgery,(38) which is in line with the lack of decreased mortality from oesophageal cancer in the present study. Antireflux surgery seems to reduce the incidence of laryngeal and pharyngeal squamous cell carcinoma,(39) which supports the present study's finding of a decreased risk of mortality from these tumours.

This population-based study shows a low rate of short-term mortality after antireflux surgery, particularly after laparoscopic fundoplication, indicating high safety of antireflux surgery in the treatment of reflux oesophagitis and Barrett's oesophagus. These findings are well in line with the low rates reported after laparoscopic fundoplication for GORD in general.(40)

Considering the limited number of studies comparing survival after antireflux surgery with antireflux medication in patients with severe GORD, more research is needed on this topic. It is too early to make any clinical recommendations before the evidence becomes more substantial. However, if the findings from the present study are proven true in the light of

future investigations, they would suggest that laparoscopic fundoplication should remain a valuable treatment option in carefully selected patients with severe GORD.

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**Table 1. Characteristics of patients with reflux oesophagitis or Barrett's oesophagus having undergone antireflux surgery with fundoplication or using antireflux medication**

		<b>Antireflux surgery Number (%)</b>	<b>Antireflux medication Number (%)</b>
<b>Patients</b>		33,904 (100)	206,322 (100)*
<b>Person-years</b>		445,594 (100)	1,851,087 (100)
<b>Sex</b>			
	Men	19,757 (58.3)	119,255 (57.8)
	Women	14,147 (41.7)	87,067 (42.2)
<b>Age at inclusion</b>			
	<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)
<b>Calendar period at inclusion</b>			
	1980 - 1989	2,871 (8.5)	18,458 (8.9)
	1990 - 1999	12,595 (37.1)	50,645 (24.5)
	2000 - 2014	18,438 (54.4)	137,219 (66.5)
<b>Charlson Comorbidity Index score</b>			
	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)
<b>Surgical approach (1996 – 2014)†</b>			
	Any approach	23,405 (69.0) [100]	Not applicable
	Laparoscopic approach	21,231 [90.7]	Not applicable
	Open approach	2,332 [8.9]	Not applicable
	Converted to open	93 [0.4]	Not applicable
<b>Causes of mortality</b>			
	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)
	Oesophageal 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.

† Restricted to the study period 1996-2014, from which data on antireflux surgery approach were available.

**Table 2. All-cause mortality among patients with reflux oesophagitis or Barrett’s oesophagus after antireflux surgery with fundoplication or antireflux medication, presented as hazard ratios (HR) with 95% confidence intervals (CI), with categorization by follow-up time, sex, age and comorbidity**

All-cause mortality	Antireflux medication			Antireflux surgery			
	Person-years	Deaths (n)	HR (95% CI)	Person-years	Deaths (n)	Crude HR (95% CI)	Adjusted <sup>†</sup> HR (95% CI)
<b>Follow-up (years)</b>							
0-34	1,851,087	39,390	1.00 (reference)	445,594	4,496	0.46 (0.45-0.48)	0.61 (0.58-0.63)
0-5	820,023	15,697	1.00 (reference)	160,961	784	0.26 (0.24-0.28)	0.41 (0.38-0.45)
>5-10	533,776	9,121	1.00 (reference)	134,328	991	0.43 (0.40-0.46)	0.54 (0.50-0.58)
>10-15	292,774	6,871	1.00 (reference)	89,095	1,116	0.53 (0.50-0.57)	0.63 (0.59-0.68)
>15	204,513	7,701	1.00 (reference)	61,209	1,605	0.71 (0.67-0.75)	0.76 (0.72-0.81)
<b>Sex</b>							
Men	1,068,442	25,936	1.00 (reference)	26,785	2,906	0.44 (0.42-0.45)	0.59 (0.56-0.61)
Women	782,645	13,454	1.00 (reference)	178,009	1,595	0.51 (0.48-0.53)	0.64 (0.61-0.68)
<b>Age at inclusion (years)</b>							
<50	857,974	7,771	1.00 (reference)	229,931	1,125	0.53 (0.50-0.57)	0.62 (0.57-0.66)
50-<65	744,085	18,511	1.00 (reference)	181,209	2,255	0.48 (0.45-0.50)	0.59 (0.56-0.62)
≥65	249,028	13,108	1.00 (reference)	34,454	1,116	0.56 (0.53-0.60)	0.65 (0.61-0.70)
<b>Charlson Comorbidity Index score</b>							
0	1,625,326	25,430	1.00 (reference)	417,213	3,905	0.56 (0.54-0.58)	0.62 (0.59-0.64)
1	189,327	9,765	1.00 (reference)	26,207	505	0.38 (0.35-0.42)	0.48 (0.44-0.53)
≥2	36,434	4,195	1.00 (reference)	2,174	86	0.37 (0.30-0.46)	0.47 (0.37-0.58)

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

**Table 3. All-cause mortality among patients with reflux oesophagitis or Barrett’s oesophagus after laparoscopic or open antireflux surgery with fundoplication, or antireflux medication, presented as hazard ratios (HR) with 95% confidence intervals (CI), with categorization by follow-up, sex, age and comorbidity**

All-cause mortality	Antireflux medication		Laparoscopic antireflux surgery		Open antireflux surgery	
	Deaths (n) / Person-years	HR (95% CI)	Deaths (n) / Person-years	Adjusted <sup>†</sup> HR (95% CI)	Deaths (n) / Person-years	Adjusted <sup>†</sup> HR (95% CI)
<b>Follow-up (years)</b>						
0-34	17,084/1,175,176	1.00 (reference)	1,105/218,813	0.56 (0.52-0.60)	251/28,292	0.80 (0.70-0.91)
0-5	9,328/630,139	1.00 (reference)	327/99,209	0.45 (0.40-0.51)	67/11,177	0.70 (0.54-0.89)
>5-10	4,831/370,977	1.00 (reference)	404/76,756	0.55 (0.48-0.63)	81/9,555	0.72 (0.56-0.92)
>10-15	2,547/152,771	1.00 (reference)	324/38,550	0.65 (0.56-0.76)	83/6,401	0.82 (0.63-1.06)
>15	378/21,288	1.00 (reference)	50/4,299	0.82 (0.54-1.23)	20/1,159	1.08 (0.60-1.94)
<b>Sex</b>						
Men	11,223/659,885	1.00 (reference)	709/126,331	0.56 (0.51-0.62)	142/15,615	0.73 (0.61-0.88)
Women	5,861/515,291	1.00 (reference)	396/92,482	0.53 (0.47-0.60)	109/12,677	0.90 (0.73-1.11)
<b>Age at inclusion (years)</b>						
<50	2,749/523,638	1.00 (reference)	319/117,687	0.64 (0.55-0.74)	54/12,572	1.05 (0.78-1.41)
50-<65	8,629/496,314	1.00 (reference)	569/87,940	0.51 (0.46-0.57)	128/12,827	0.76 (0.62-0.92)
≥65	5,706/155,225	1.00 (reference)	217/13,185	0.56 (0.47-0.66)	69/2,893	0.76 (0.58-0.98)
<b>Charlson Comorbidity Index score</b>						
0	10,126/1,040,706	1.00 (reference)	929/203,597	0.61 (0.56-0.67)	206/25,867	0.89 (0.76-1.04)
1	4,581/111,339	1.00 (reference)	158/14,070	0.41 (0.35-0.50)	34/2,205	0.54 (0.38-0.77)
≥2	2,377/23,131	1.00 (reference)	18/1,146	0.25 (0.15-0.40)	11/220	0.65 (0.35-1.19)

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

**Table 4. Disease-specific mortality among patients with reflux oesophagitis or Barrett's oesophagus after antireflux surgery with fundoplication or antireflux medication, presented as hazard ratios (HR) with 95% confidence intervals (CI), categorized according to follow-up time**

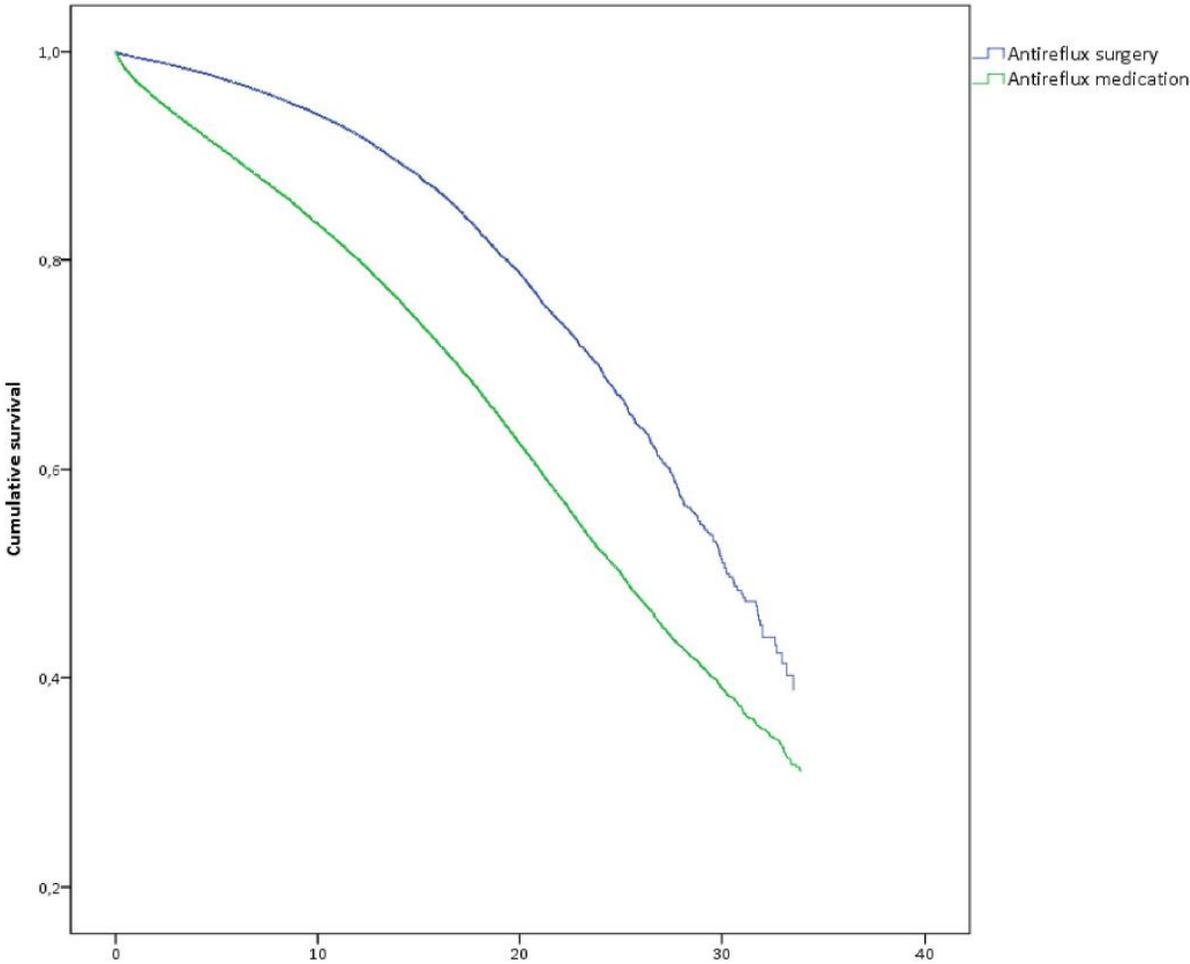
Cause of death	Antireflux medication		Antireflux surgery		
	Deaths (n)	HR (95% CI)	Deaths (n)	Crude HR (95% CI)	Adjusted <sup>†</sup> HR (95% CI)
<b>Cardiovascular disease</b>					
Follow-up (years)					
0-34	19,102	1.00 (reference)	2,159	0.45 (0.43-0.47)	0.58 (0.55-0.61)
0-5	6,714	1.00 (reference)	286	0.22 (0.20-0.25)	0.37 (0.32-0.42)
>5-10	4,478	1.00 (reference)	441	0.39 (0.36-0.43)	0.49 (0.44-0.55)
>10-15	3,609	1.00 (reference)	557	0.50 (0.46-0.55)	0.59 (0.53-0.66)
>15	4,301	1.00 (reference)	875	0.69 (0.64-0.75)	0.72 (0.66-0.78)
<b>Respiratory disease</b>					
Follow-up (years)					
0-34	10,229	1.00 (reference)	1,154	0.44 (0.42-0.47)	0.62 (0.57-0.66)
0-5	3,404	1.00 (reference)	130	0.20 (0.17-0.23)	0.36 (0.30-0.44)
>5-10	2,440	1.00 (reference)	214	0.35 (0.30-0.40)	0.48 (0.41-0.57)
>10-15	2,003	1.00 (reference)	294	0.48 (0.42-0.54)	0.60 (0.52-0.69)
>15	2,382	1.00 (reference)	516	0.74 (0.67-0.82)	0.82 (0.74-0.92)
<b>Oesophageal cancer</b>					
Follow-up (years)					
0-34	964	1.00 (reference)	158	0.69 (0.58-0.82)	1.05 (0.87-1.28)
0-5	503	1.00 (reference)	28	0.29 (0.20-0.43)	0.56 (0.37-0.84)
>5-10	178	1.00 (reference)	32	0.71 (0.49-1.03)	1.25 (0.83-1.89)
>10-15	142	1.00 (reference)	52	1.20 (0.87-1.65)	1.82 (1.27-2.61)
>15	141	1.00 (reference)	46	1.13 (0.81-1.58)	1.09 (0.74-1.60)
<b>Laryngeal or pharyngeal cancer</b>					
Follow-up (years)					
0-34	270	1.00 (reference)	13	0.19 (0.11-0.33)	0.35 (0.19-0.65)
0-5	93	1.00 (reference)	3	0.17 (0.05-0.52)	0.43 (0.13-1.48)
>5-10	77	1.00 (reference)	5	0.26 (0.10-0.63)	0.67 (0.27-1.67)
>10-15	51	1.00 (reference)	3	0.20 (0.06-0.62)	0.21 (0.05-0.80)
>15	49	1.00 (reference)	2	0.14 (0.03-0.56)	0.18 (0.04-0.81)
<b>Lung cancer</b>					
Follow-up (years)					
0-34	2,253	1.00 (reference)	257	0.45 (0.40-0.51)	0.67 (0.58-0.80)
0-5	771	1.00 (reference)	34	0.23 (0.16-0.32)	0.41 (0.28-0.61)
>5-10	616	1.00 (reference)	71	0.46 (0.36-0.58)	0.75 (0.56-0.99)
>10-15	438	1.00 (reference)	76	0.57 (0.45-0.73)	0.76 (0.56-1.01)
>15	428	1.00 (reference)	76	0.60 (0.47-0.77)	0.72 (0.54-0.94)

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† Adjusted for sex, age, calendar period, country of residence, and Charlson Comorbidity Index score.

# Figure legends

Figure 1. Kaplan-Meier survival plot of all-cause mortality in patients with reflux esophagitis or Barrett's oesophagus having undergone antireflux surgery with fundoplication or using antireflux medication.



**Supplementary Table 1. Codes defining cohort members with reflux oesophagitis or Barrett's oesophagus and those who had undergone antireflux surgery with fundoplication**

	Sweden	Finland	Denmark	Iceland
<b>Severe gastro-oesophageal reflux disease</b>				
Reflux oesophagitis	ICD-8: 530.93, 530.94 ICD-9: 530B, 530C ICD-10: K21.0	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
Barrett's oesophagus	ICD-10: K22.7	ICD-9: 5301B ICD-10: K22.7	ICD-10: DK22.7	ICD-10: 22.7
<b>Any antireflux surgery</b>				
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
Other surgeries of the diaphragm and due to gastro-oesophageal reflux disease	JBW96, JBW97	JBW96, JBW97	KJBW96, KJBW97	JBW96, JBW97
<b>Laparoscopic antireflux surgery</b>				
Laparoscopic antireflux surgery	JBC01	JBC01	KJBC01	JBC01
Other laparoscopic surgery of the diaphragm and due to gastro-oesophageal reflux disease	JBW97	JBW96, JBW97	KJBW96, KJBW97	JBW96, JBW97

**Supplementary Table 2. Codes defining cardiovascular disease, respiratory disease, and cancer of the oesophagus and cardia, larynx and pharynx, and bronchus and lung in the cause of death registries**

	<b>Cardiovascular</b>	<b>Respiratory</b>	<b>Oesophagus and cardia</b>	<b>Larynx and pharynx</b>	<b>Bronchus and lung</b>
ICD-8	390 to 458 <sup>a</sup>	460 to 519 <sup>a</sup>	150 <sup>a</sup> 151.01 <sup>d</sup>	146 to 148 <sup>a</sup> 161 <sup>a</sup>	162.1 <sup>c</sup>
ICD-9	390 to 459 <sup>a</sup>	460 to 519 <sup>a</sup>	150 <sup>a</sup> 151A <sup>b</sup>	146 to 148 <sup>a</sup> 161 <sup>a</sup>	162C to 162X <sup>b</sup>
ICD-10	I00 to I99 <sup>a</sup>	J00 to J99 <sup>a</sup>	C15 to C16 <sup>a</sup>	C09 to C13 <sup>a</sup> C32 <sup>a</sup>	C34 <sup>a</sup>

a All with correct first 3 positions

b All with correct first 4 positions

c All with correct first 5 positions

d All with correct first 6 positions