BMJ Open

Cohort profile: the Nordic Antireflux Surgery Cohort (NordASCo)

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To cite: Maret-Ouda J, Wahlin K, Artama M, *et al*. Cohort profile: the Nordic Antireflux Surgery Cohort (NordASCo). *BMJ Open* 2017;**7**:e016505. doi:10.1136/bmjopen-2017-016505

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-016505)

Received 19 February 2017
Revised 8 April 2017
Accepted 26 April 2017

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ABSTRACT

Purpose To describe a newly created all-Nordic cohort of patients with gastro-oesophageal reflux disease (GORD), entitled the Nordic Antireflux Surgery Cohort (NordASCo), which will be used to compare participants having undergone antireflux surgery with those who have not regarding risk of cancers, other diseases and mortality.

Participants Included were individuals with a GORD diagnosis recorded in any of the nationwide patient registries in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) in 1964–2014 (with various start and end years in different countries). Data regarding cancer, other diseases and mortality were retrieved from the nationwide registries for cancer, patients and causes of death, respectively.

Findings to date The NordASCo includes 945 153 individuals with a diagnosis of GORD. Of these, 48 433 (5.1%) have undergone primary antireflux surgery. Median age at primary antireflux surgery ranged from 47 to 52 years in the different countries. The coding practices of GORD seem to have differed between the Nordic countries.

Future plans The NordASCo will initially be used to analyse the risk of developing known or potential GORD-related cancers, that is, tumours of the oesophagus, stomach, larynx, pharynx and lung, and to evaluate the mortality in the short-term and long-term perspectives. Additionally, the cohort will be used to evaluate the risk of non-malignant respiratory conditions that might be caused by aspiration of gastric contents.

Strengths and limitations of this study

- The main strength of the Nordic Antireflux Surgery Cohort is the large number of individuals included, constituting the largest cohort to date of patients who have undergone antireflux surgery.
- The population-based design counteracts selection bias and facilitates the generalisability of the findings.
- The long and complete follow-up in the registries enables studies of conditions with an expected long latency interval between antireflux surgery and disease.
- There are variations in clinical practice and coding of diagnoses and procedures between the countries, including the codes associated with gastro-oesophageal reflux disease and antireflux surgery.

INTRODUCTION

The Nordic Antireflux Surgery Cohort (NordASCo) was set up with the purpose of examining the consequences of surgery for gastro-oesophageal reflux disease (GORD). GORD is defined as a 'condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications'.[1] GORD can occur as a result of pathological levels of regurgitation of acidic stomach contents, often also including alkaline bile salts and pancreatic enzymes, into the oesophagus. The primary symptoms of GORD are heartburn and regurgitation of stomach contents.[2] Other, less common symptoms include chest pain, nausea, hoarseness and symptoms associated with bronchial aspiration of reflux contents reaching the oropharynx, for example, pneumonia, cough and other respiratory disorders.[2] The prevalence of GORD is estimated at 10%–20% in the USA and Europe, and less than 5% in Asia.[3] The prevalence has increased during the last few decades,[4] an increase that correlates with the increasing prevalence of obesity, a known risk factor for developing GORD.[5–7] Other established risk factors for GORD are heredity and tobacco smoking.[8–11] GORD can lead to complications, including erosive oesophagitis, oesophageal strictures, premalignant Barrett's oesophagus and oesophageal adenocarcinoma.[2] The primary treatment is medical, most often using a proton pump inhibitor. An alternative but less often used treatment is antireflux surgery, during which the fundus of the stomach is wrapped partly or completely around the lower oesophagus, mechanically hindering GORD.[2] Antireflux surgery should be considered in patients with severe GORD or poor response to medical treatment, especially in young, physically fit and healthy adults in whom pharmacological treatment otherwise would be necessary for a long period of time.[12]

The aim of the current paper is to describe the NordASCo. The cohort was created to evaluate how antireflux surgery influences the risks for certain cancers and other conditions related to GORD, with the potential to identify preventive measures. Another aim of the creation of the cohort is to evaluate the safety of antireflux surgery regarding short-term and long-term mortality and morbidity, as well as postoperative complications.

COHORT DESCRIPTION

The NordASCo is based on merged data from nationwide health data registries from all five Nordic countries, that is, Denmark (excluding Greenland and the Faroe Islands), Finland, Iceland, Norway and Sweden. The principal study design used in the current cohort has previously been described in detail elsewhere.[13] The study design is feasible since all the Nordic countries maintain registries of similar structure and contents that include the entire population of each country. Additionally, all Nordic countries maintain personal identifiers for all individuals in the populations, which makes it possible to link all individuals' data between different registries. The registries used for constructing the NordASCo were the patient registries, cancer registries and the causes of death registries. These registries have been described in detail elsewhere,[14–18] and only a brief description is provided here.

The patient registries

The patient registries of the Nordic countries were founded in different years, and reached complete national coverage in 1978 (Denmark), 1967 (Finland), 1999 (Iceland), 1997 (Norway) and 1987 (Sweden). The patient registries contain codes for diagnoses and surgical procedures from all inpatient and specialised outpatient care, as well as dates related to hospital stays and outpatient appointments. The patient registries also contain diagnoses of oesophagitis and Barrett's oesophagus, of value for future studies regarding the progression to oesophageal adenocarcinoma. Validation studies conducted on the patient registries have found the completeness and accuracy to be high. In Denmark, the positive predictive value has been found to range between 15% and 100% depending on the diagnosis, although the lowest positive predictive values were found among gynaecological diagnoses, not assessed in the current study.[14] In Finland, the positive predictive value was 75%–99% for common diagnoses.[19] In Sweden, the positive predictive value has been found to range between 85% and 95% for common diagnoses.[15]

The cancer registries

The cancer registries in the Nordic countries contain anatomical and histological coding of all tumours and date of diagnosis. Moreover, in many cases, data for how the malignancy was found and tumour stage are also available. The cancer registry in Denmark was founded in 1942, with mandatory registration since 1987. The cancer registry in Finland was founded in 1953, with mandatory registration since 1961. In Norway, Iceland and Sweden, the cancer registries were founded in 1951, 1954 and 1958, respectively, with mandatory reporting since 1953 in Norway, and since their initiation in Iceland and Sweden. The cancer registries have been validated in several studies, and both completeness and accuracy of data have been deemed to be high. In Iceland, the completeness has been found to be 99.2%, and 96.4% of the tumours were morphologically verified.[20] The completeness in Norway has been found to be 98.8%, with 93.8% morphologically verified.[16] In Sweden, approximately 98% of all malignancies in the cancer registry are morphologically verified, and the completeness of tumour stage has been found to be 98.2%.[17 21]

The causes of death registries

The causes of death registries include date and causes of death, including underlying causes of death. These registries have been nationwide since their initiation in all Nordic countries. The causes of death registries in Denmark, Finland, Iceland, Norway and Sweden have been electronically available since 1970, 1969, 1952, 1951 and 1961, respectively.

PERMISSIONS

Ethical permissions were retrieved from the relevant ethical committees in Iceland, Norway and Sweden (permissions VSN-14–083, 2014/1498–3, 2014/234–31 and 2015/240–32, respectively). Ethical permissions are not required in Denmark and Finland for this type of register-based research. Permissions to use the registry data for the NordASCo were retrieved from the Data Protection Authorities of Denmark and Iceland (permissions 2014-41-3503 and 2014050845, respectively), and in Finland from the National Institute for Health and Welfare, Statistics Finland and the Population Register Centre (permissions THL/1404/5.05.00/2014, TK53-1555-15 and 2345/410/15). Due to data regulations in Denmark, data from Danish registries are not allowed to leave Denmark. Therefore, the data from the other participating countries were sent to the governmental agency Statistics Denmark to allow further data management. All data management and analyses are conducted on safe servers belonging to Statistics Denmark, accessed externally through a safe virtual private network.

PARTICIPANTS

The individuals included in the NordASCo were selected based on a recorded diagnosis of GORD in the patient registries when these registries were available at the time of data retrieval, that is, between 1 July 1979 and 31 December 2014 in Denmark, 1 January 1968 and 31 December 2014 in Finland, 1 January 2000 and 31 December 2013 in Iceland, 1 January 2007 and 31 December 2013 in Norway, and between 1 January 1964 and 31 December 2013 in Sweden. All cohort members

needed to be above 18 years of age at the time of their first GORD diagnosis or primary antireflux surgery. The codes used to identify patients with GORD were 530.90, 539.11, 539.12, 560.40, 551.30, 551.39, 784.30 and 784.39 in the International Statistical Classification of Diseases and Related Health Problems version 7 (ICD-7), 78430, 55130, 53093 and 53094 in the ICD-8, 7871A, 787B, 5513A, 553D, 530B-C, 5301A-D and 5301X in the ICD-9, and K20, K21, K22.7, K44 and R12 in the ICD-10.

Following the identification of individuals for the NordASCo, they were linked using their personal identity codes to the causes of death registry and the cancer registry of each country. Before the delivery of data from each country to Statistics Denmark, any identifiable data (such as personal identity codes and names) were removed, and instead all patients were assigned an arbitrary code number to enable future linkages between registries. Following delivery, all data were checked for correctness and completeness, and to ascertain that no personally identifiable variables were left. Thereafter, the data from the different registries within each country were merged, and subsequently the data from all countries were merged into one final database, the NordASCo.

The cohort members were categorised into an 'exposed group', that is, those who underwent primary antireflux surgery (open or laparoscopic), and an 'unexposed group', that is, those who did not undergo such surgery during the study period. The operation codes defining cohort members who underwent antireflux surgery were 4054, 4056, 4074, 4076, 4080 and 4084 in the ICD-7. Following the implementation of the Nordic Medico-Statistical Committee (NOMESCO) surgical codes in the year 1997, JBC and JBW were used. Moreover, older Finnish and Swedish surgical codes were used to identify antireflux surgery before the ICD-7 (6241, 6242, 6249, 6251 and 6259 in Finland, and 4272 in Sweden).

Variables and data management

The main variables in the NordASCo are shown in figure 1. Further, the data management of the patient registries is shown in figure 2. Exact date of birth was lacking in Sweden and Norway, due to data handling regulations only permitting delivery of year and month of birth. Due to this, the 15th of each month was set as the date of birth in these countries. Data were retrieved from as long as possible back in time, limited by the year of initiation and nationwide coverage of the patient registries in each country. All cohort members were followed up through the relevant registries until the date of the outcome of interest in each study, death or end of the study period, whichever occurred first. The patient registries in the various countries were retrieved until varying end dates, mainly due to the date of submission of the data order. The maximum follow-up was therefore until the end of the year 2013 for Iceland, Norway and Sweden, and the end of 2014 for Denmark and Finland. The arbitrary

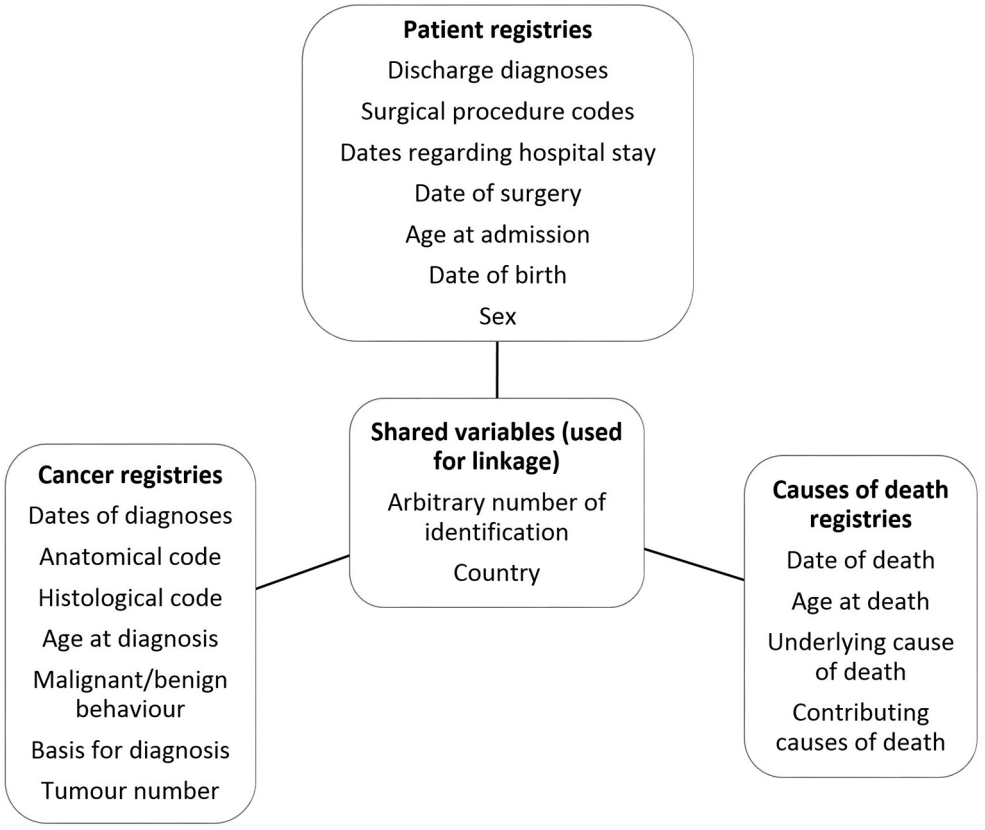

Figure 1 Variables used from different registries within each Nordic country for participants of the Nordic Antireflux Surgery Cohort.

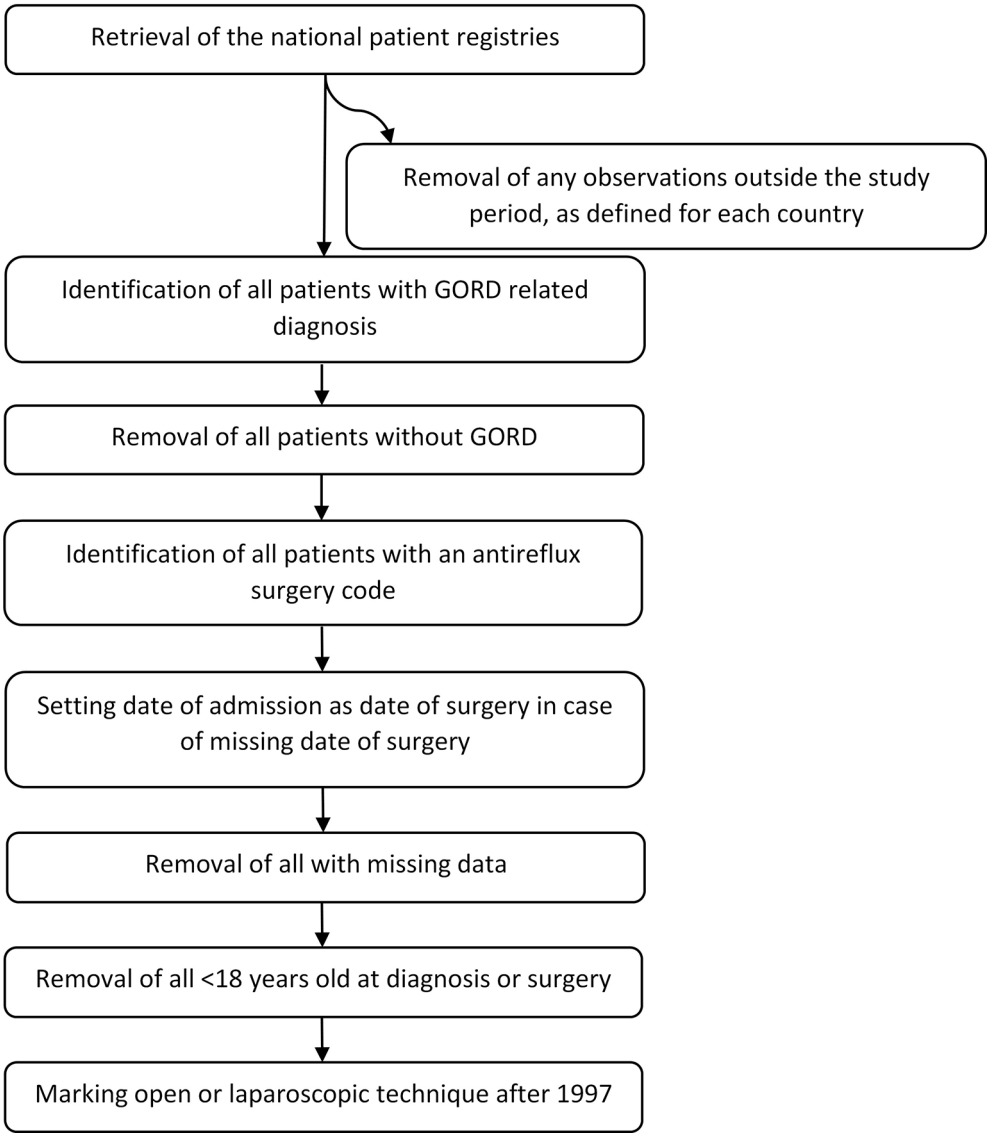

Figure 2 Data management of the patient registries in the Nordic Antireflux Surgery Cohort. GORD, gastro-oesophageal reflux disease.

numbers that were used to replace the personal identity codes used for linkage are kept in each of the relevant agencies in each country. These arbitrary numbers can be used for future follow-up of all cohort members as well as adding data from additional registries for assessing other exposures and outcomes of interest. Furthermore, the arbitrary numbers could be used if data need to be checked regarding completeness and correctness.

STUDIES

The NordASCo will be used to measure the risk of developing known or potential GORD-related cancers following antireflux surgery. The initial focus will be on how the risk of oesophageal adenocarcinoma develops over time after surgery, compared with the risk development of oesophageal squamous cell carcinoma and gastric adenocarcinoma. Other tumours of potential interest are cancer of the larynx, pharynx and lung, which might be associated with GORD, although fewer studies support these associations and any association with lung cancer is controversial.[22–24] Additionally, the NordASCo will be used to evaluate whether antireflux surgery decreases the risk of non-malignant conditions that might be caused by aspiration of acidic gastric contents, for example, asthma, pneumonia and cardiovascular morbidity and mortality.[25 26] Due to a general decrease in the number of antireflux procedures performed, with one explanation being the risk of postoperative mortality and complications following antireflux surgery, further studies are needed to assess these risks and to identify individuals who would benefit most from such surgery.

Findings to date

In total, 945 153 individuals with a GORD diagnosis have been included in the NordASCo. Characteristics of the cohort members are presented in table 1. Of all

Table 1 Characteristics of individuals included in the entire Nordic Antireflux Surgery Cohort (NordASCo), as well as the numbers and percentage within each characteristic category undergoing antireflux surgery

	Entire NordASCo Number (% distribution)	Antireflux surgery Number (% within category)
Total	945 153 (100.0)	48 433 (5.1)
Country		
Denmark	243 137 (25.7)	6912 (2.8)
Finland	42 044 (4.4)	20 328 (48.3)
Iceland	4545 (0.5)	1296 (28.5)
Norway	192 290 (20.3)	1429 (0.7)
Sweden	463 137 (49.0)	18 468 (4.0)
Sex		
Male	462 755 (49.0)	27 169 (5.9)
Female	481 280 (51.0)	21 264 (4.4)
Age at entry (in years)		
18–29	64 033 (6.8)	3395 (5.3)
30–39	94 945 (10.0)	7379 (7.8)
40–49	141 323 (15.0)	11 717 (8.3)
50–59	181 894 (19.2)	13 614 (7.5)
≥60	462 958 (49.0)	12 328 (2.7)
Calendar period (year)		
1979–1984	38 161 (4.0)	1370 (3.6)
1985–1999	189 017 (20.0)	19 855 (10.5)
2000–2014	717 975 (76.0)	27 208 (3.8)

participants, 48 433 (5.1%) underwent a primary antireflux surgery during the study period and 896 720 (94.9%) did not. The proportion of patients with a registered GORD diagnosis who underwent antireflux surgery varied between countries, and was lower in Denmark, Norway and Sweden (2.8%, 0.7% and 4.0%, respectively) compared with Finland and Iceland (48.3% and 28.5%), which might also reflect substantial differences in clinical practice and registration routines. The sex distribution was more even among both the operated and non-operated cohort members. The surgery group was generally younger (25.5% ≥60 years at entry) than the non-surgery group (50.4% ≥60 years old at entry). The median age at primary antireflux surgery ranged from 47 to 52 years in the different countries. Most cohort members were included during the time periods 1985–1999 (41.0%) and 2000–2014 (56.2%) in the antireflux surgery group, and during the time period 2000–2014 in the non-operated group (76.0%).

Figure 3 shows the annual incidence of primary antireflux surgery among adults in the Nordic countries per 100 000 inhabitants, including both open and laparoscopic techniques. The rate in Denmark and Norway remained fairly stable during the study period. For both Finland and Sweden, a plateau was seen during the end of the 1990s, followed by a decrease. In Iceland, a similar pattern was seen, but with a later peak in 2003. Due to the relatively small population in Iceland, large variations in rates were seen but with only small differences in the absolute number of procedures. The total number of primary antireflux surgery conducted per year is shown in figure 4. This figure also shows a peak in the number of primary antireflux procedures in the Nordic countries

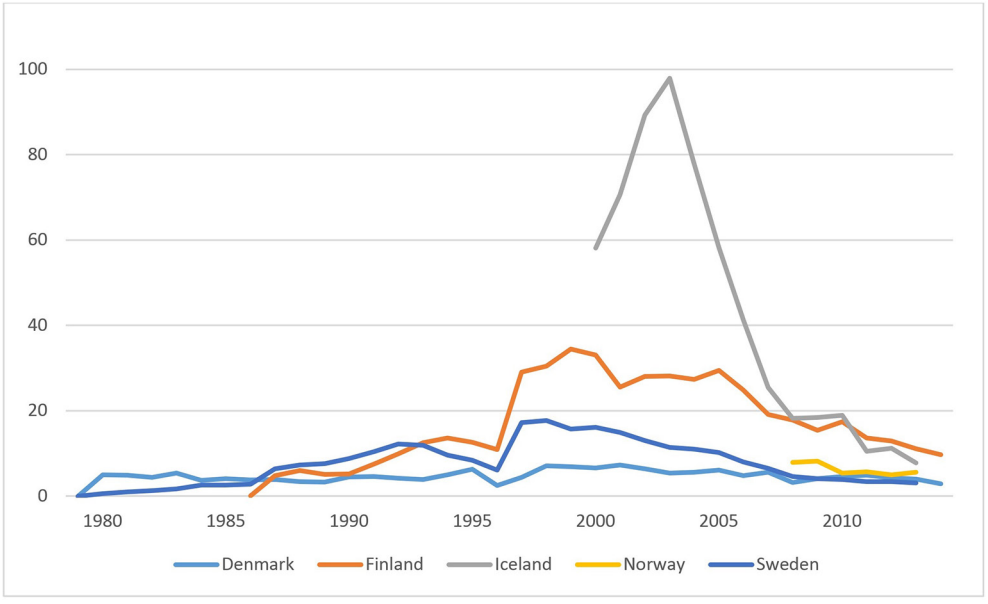

Figure 3 Rate of primary antireflux procedures per 100 000 inhabitants in the five Nordic countries of the Nordic Antireflux Surgery Cohort, in 1980–2014.

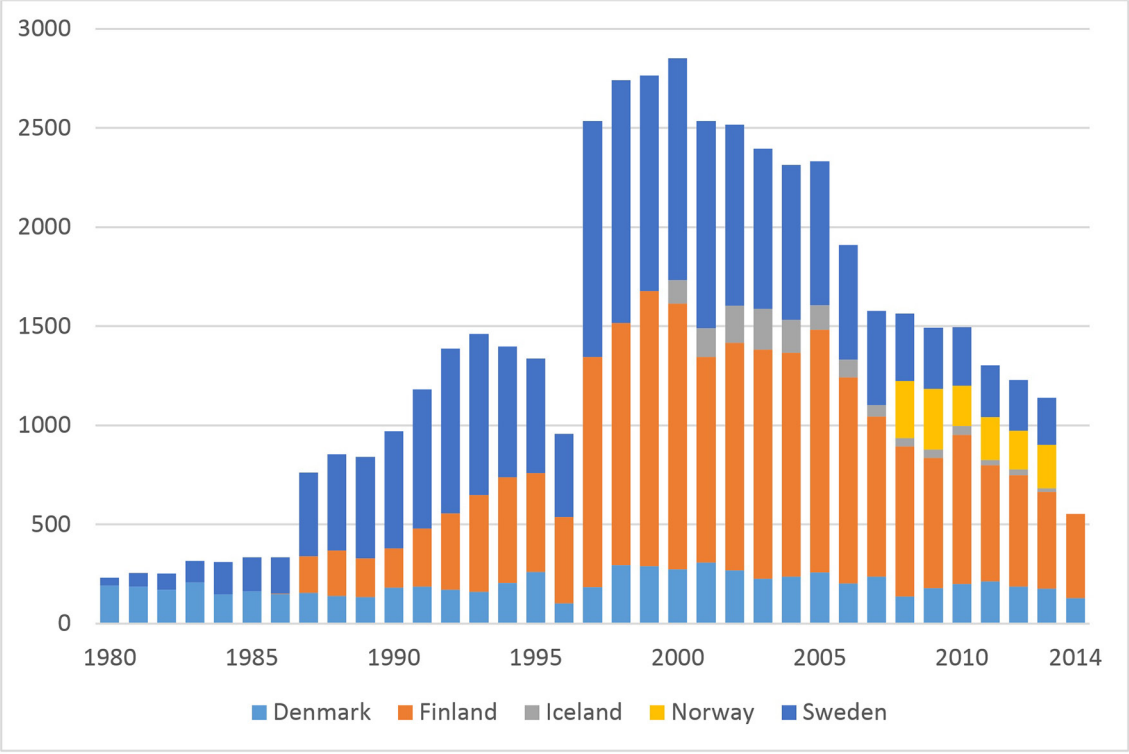

Figure 4 Total numbers of primary antireflux procedures per year in the Nordic Antireflux Surgery Cohort, in 1980–2014.

around the year 2000, followed by a decline and a stabilisation until the year 2013. The year 2014 includes data only from Denmark and Finland. The decrease in the number of procedures from 1994 to 1996, with a rebound in 1997, is most likely due to a lack of specific codes representing laparoscopic antireflux surgery before the implementation of NOMESCO. Thus, many laparoscopic procedures may have been registered using a different surgical code that was less specific, and therefore not possible to include in the current cohort.

Data regarding open or laparoscopic technique are available since 1997 (figure 5). The countries were grouped into two groups, one where data from the entire period 1997–2013 are available (Denmark, Finland and

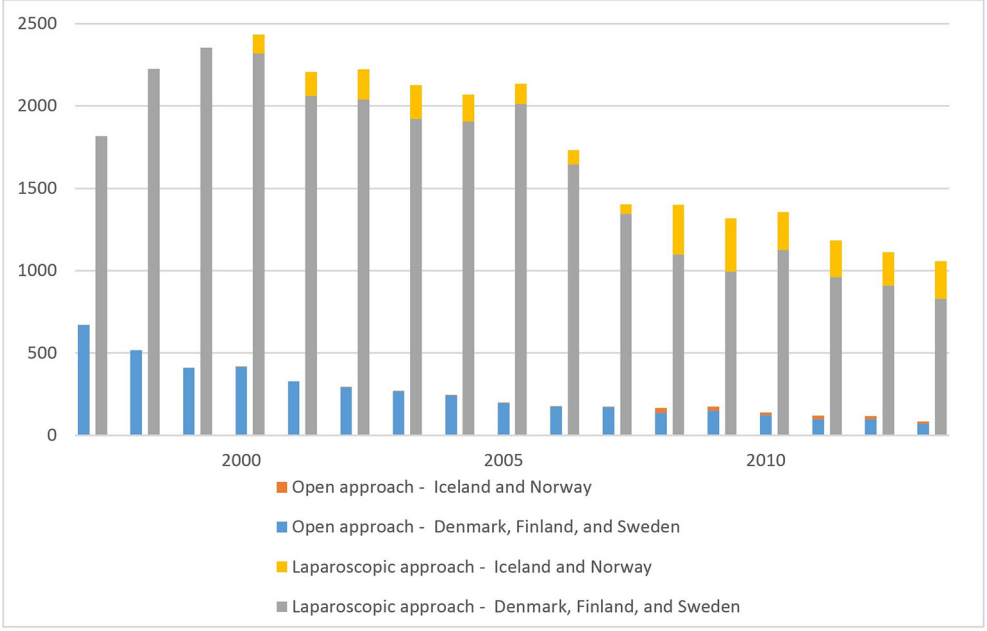

Figure 5 Number of primary antireflux procedures conducted using open or laparoscopic technique in the Nordic Antireflux Surgery Cohort, 1997–2013. Countries where data from the entire period were available are grouped (Denmark, Finland and Sweden), as are countries where only part of the study period was available (Iceland and Norway).

Sweden), and one group where all years were not available (Iceland and Norway). There was a steady decline in the number of primary antireflux procedures using open technique. An increase in the number of primary antireflux procedures conducted using laparoscopic approach was seen until the year 2000, followed by a decline, which corresponds to the general decrease in the total number of primary antireflux procedures performed.

To date, two studies have been published based on data collected for the NordASCo, although these were based on the Swedish part of the cohort only. One study assessed the short-term mortality following primary laparoscopic fundoplication in the working age population (18–65 years) during the time period 1997–2013, and revealed an almost negligible risk of mortality and low risk of reoperation.[27] The other study examined the risk of mortality following secondary antireflux surgery and identified no deaths.[28]

Strength and limitations

The main strength of the NordASCo is the large number of individuals included. This creates opportunities for subgroup analyses, for example, regarding various time intervals and disease risk following antireflux surgery. The population-based design counteracts selection bias and facilitates the generalisability of the findings. The long and complete follow-up in the registries enables studies of conditions with an expected long latency interval between antireflux surgery and disease, for example, cancer to be conducted. Furthermore, the Nordic countries have similarities in their publicly financed healthcare systems and have comparable demographic and socioeconomic characteristics of the populations. Virtually all diagnoses and surgical procedures with defined codes are available for the members of the NordASCo.

Among the main weaknesses is the potential variation in clinical practice and coding of diagnoses and procedures between countries, including the codes associated with GORD and antireflux surgery. This can be seen in the varying proportions of codes representing GORD and antireflux surgery from each country. For example, 48.3% of the patients with a GORD diagnosis in Finland underwent antireflux surgery, but the GORD group only constitutes 4.4% of the entire NordASCo. In Norway, on the other hand, a limited 0.7% of patients with GORD underwent antireflux surgery, but patients with GORD represent 20.3% of the entire NordASCo. This could mean that only the most severe cases of GORD requiring inpatient healthcare will receive such a diagnostic code in Finland. This would, however, lead to an underestimation of the number of individuals in the non-operated GORD group, and selection of the more severe cases, thus leading to an underestimation of any preventive effect of antireflux surgery. However the accuracy of the GORD diagnosis when recorded should be good. The main reason for discrepancies is probably non-recording of GORD diagnosis, which is not a major methodological issue in this cohort study. Nevertheless, adjustment or stratification for country might be justified in future studies based on this cohort. Furthermore, subanalyses of patients with severe GORD (Barrett's oesophagus or oesophagitis), where more objective measurements are used for diagnosis, would be valuable. Another limitation is the lack of data on potential variables of relevance for the conditions studied, for example, medication and lifestyle exposures, including body mass index, tobacco smoking and dietary factors.

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Collaborators We invite researchers with interests related to the diseases included in the NordASCo to contact the research group for discussion regarding collaborative research. Researchers interested in collaborating in exploring the cohort data are welcome to contact Professor Lagergren, Chief Investigator of the NordASCo.

Contributors JMO, MA, NB, MF, EL, EP, PR, LT, MvEC and JL handled the permissions and data collection within each country. JMO, KW, FM, MvEC and JL handled the data management, merging of the data sets and analyses. JMO drafted the manuscript. JMO, KW, MA, NB, MF, EL, FM, EP, PR, LT, MvEC and JL revised the manuscript for important intellectual content. JL was responsible for the final version of the manuscript.

Funding This work was supported by the Swedish Research Council [D0547801], the Swedish Cancer Society [2015/460] and the Nordic Cancer Union [186058]. The grant providers had no role in the design, conduction, analysis or reporting of the cohort.

Competing interests None declared.

Ethics approval Ethical committees in Iceland, Norway and Sweden (permissions VSN-14-083, 2014/1498-3, 2014/234-31 and 2015/240-32, respectively). The Data Protection Authorities of Denmark and Iceland (permissions 2014-41-3503 and 2014050845, respectively), and in Finland from the National Institute for Health and Welfare, Statistics Finland and the Population Register Centre (permissions THL/1404/5.05.00/2014, TK53-1555-15 and 2345/410/15).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Due to strict data management regulations in Denmark, the data are stored on servers within Statistics Denmark. The data cannot be accessed by potential new collaborators without permission from the original data holders in each of the countries, and access to the data at Statistics Denmark is restricted.

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