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ORIGINAL ARTICLE

Cohort profile: Nordic Helicobacter Pylori eradication project (NordHePEP)

Anna-Klara Pettersson[a], Giola Santoni[a], Jacinth Yan[b], Cecilia Radkiewicz[a], Shaohua Xie[a], Helgi Birgisson[c], Eivind Ness-Jensen[a,d,e], My von Euler-Chelpin[f], Joonas H. Kauppila[a,g] and Jesper Lagergren[a,h]

[a]Department of Molecular medicine and Surgery, Karolinska Institutet, Upper Gastrointestinal Surgery, Stockholm, Sweden; [b]Division of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [c]The Icelandic Cancer Registry, Reykjavik, Iceland; [d]Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway; [e]Medical Department, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway; [f]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [g]Department of Surgery, Oulu University Hospital and University of Oulu, Oulu, Finland; [h]School of Cancer and Pharmaceutical Sciences, King's College London, London, UK

ABSTRACT

Purpose: This cohort description presents the Nordic Helicobacter Pylori Eradication Project (NordHePEP), a population-based cohort of patients having received eradication treatment for Helicobacter pylori (HP). The cohort is created with the main purpose of examining whether and to what extent HP eradication treatment influences the risk of gastrointestinal cancer.

Participants: NordHePEP includes all adults (aged ≥18 years) having been prescribed and dispensed HP eradication treatment according to the nationwide complete drug registries in any of the five Nordic countries (Denmark, Finland, Iceland, Norway, or Sweden) between 1994 and 2020 (start and end year varies between countries). We have retrieved and merged individual-level data from multiple national registries, including drug, patient, cancer, population, and death registries.

Findings: The cohort includes 674,771 patients having received HP eradication treatment. During up to 23 years of follow-up, 59,292 (8.8%) participants were diagnosed with cancer (non-melanoma skin cancer excluded), whereof 15,496 (2.3%) in the gastrointestinal tract.

Future plans: We will analyse HP eradication treatment in relation to gastrointestinal cancer risk. Standardised incidence ratios will be calculated as the *observed* cancer incidence in the cohort divided by the *expected* cancer incidence, derived from the background population of the corresponding age, sex, and calendar year.

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Introduction

The Nordic Helicobacter Eradication Project (NordHePEP) is a multinational population-based cohort, created with the overarching aim to examine whether and to what extent eradication of infection with Helicobacter pylori (HP) influences the risk of developing gastrointestinal cancer. HP is a gram-negative bacterium that commonly infects or colonises the human stomach, usually in early childhood, and remains lifelong if left untreated [1]. Although the prevalence of HP infection is decreasing in many countries, the total global prevalence is >50% but varies widely between geographical regions. HP infection is associated with dense living conditions and poor hygiene practices, and the highest prevalence (85–95%) is reported in developing countries [2,3].

HP infection can cause gastritis and gastric ulcerations and might develop into atrophy and metaplasia of the mucosa, and ultimately progress into invasive cancer [4]. A strong and causal association between HP infection and gastric adenocarcinoma is well established, with the World Health Organisation (WHO) classifying HP as a class I carcinogen and the single most carcinogenic infectious agent, responsible for approximately 770,000 gastric cancer deaths worldwide each year [5,6]. On the other hand, HP-associated gastric atrophy may counteract gastro-oesophageal reflux, the main risk factor for oesophageal adenocarcinoma, by suppressing acid production of the parietal cells in the stomach mucosa. Consequently, HP infection is associated with a decreased risk of oesophageal adenocarcinoma [7–9]. The decreasing gastric adenocarcinoma incidence and the concomitant rise in oesophageal adenocarcinoma incidence seen in many Western countries over the last decades could be partly attributable to the decrease in HP prevalence.

The fact that HP infection alters the gastric microbiota and increases intragastric pH levels promotes the growth of acid-sensitive bacteria throughout the gastrointestinal tract. Thus, HP infection does not only affect the local gastric environment but can also alter the microbiota homeostasis in all parts of the gastrointestinal tract [10]. Therefore, it is

CONTACT Jesper Lagergren jesper.lagergren@ki.se Department of Molecular medicine and Surgery, Karolinska Institutet, Upper gastrointestinal surgery, Retzius Street 13a, Stockholm, 171 77, Sweden

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not surprising that emerging evidence indicates that HP infection also influences the risk of cancer of the liver, pancreas, biliary tract, and colorectum [11–14].

The main indication of HP eradication is treatment and prevention of gastritis or peptic ulcers in HP-infected patients. The most commonly recommended first-line HP eradication treatment is *standard triple treatment,* consisting of a 7-day (or longer) regimen with a proton pump inhibitor combined with at least two of the three antibiotics clarithromycin, amoxicillin, or metronidazole (Supplementary Table S1) [15]. Clinical guidelines differ between geographical regions, primarily depending on varying HP resistance patterns to clarithromycin and metronidazole. In the Nordic countries, such resistance is uncommon and the standard triple treatment is recommended, accomplishing an eradication rate of 80–90% [16,17].

In addition to the well-established effect on HP-associated gastritis and ulcers, HP eradication treatment reduces the risk of gastric adenocarcinoma by approximately 50% in endemic countries [18,19]. But studies on how HP eradication influences the risk of gastric adenocarcinoma in Western populations are scarce, where the demographic composition and HP prevalence and virulence are different compared to endemic areas. Importantly, the influence of HP eradication treatment on the risk of oesophageal adenocarcinoma and other gastrointestinal cancer types is largely unknown, independent of geographical region [20].

We aimed to describe the NordHePEP in detail and provide a reference paper for future analytic studies using data from the cohort, and also to open the cohort for other research purposes.

Cohort description

NordHePEP includes all adult (age ≥18 years) Nordic residents having received HP eradication treatment according to the national prescribed drug registry in Denmark, Finland, Iceland, Norway, or Sweden (alphabetic order), between 1994 and 2020. In order to collect detailed information on relevant covariates and outcomes, each of the individuals included in the cohort have been linked to multiple other nationwide Nordic health data and demographic registries. These linkages are enabled by the unique personal identity number assigned to all Nordic residents. The structure and content of the registries used in the present cohort are similar in all Nordic countries [21], and these data sources are described below.

Data sources

NordHePEP contains clinical and demographic data derived from five types of national registries in each of the five Nordic countries.

1. The *prescribed drug registries* contain information on all medications dispensed by prescription and purchased at a pharmacy [22,23]. Medications are recorded according to the Anatomical Therapeutic Chemical Classification (ATC) system, developed by WHO to facilitate drug use statistics and research [24]. The start year of nationwide completeness varies between countries and is 1994 in Denmark and Finland, 2002 in Iceland, 2004 in Norway, and 2005 in Sweden. Data are automatically and directly transferred from the pharmacies into the registries, assuring a close to 100% completeness [25].

2. *The patient* (hospital discharge) *registries* record all inpatient care and specialised outpatient care visits. These registries reached complete nationwide coverage and data on personal identity numbers in years 1967 in Finland, 1978 in Denmark, 1987 in Sweden, 1999 in Iceland, and 2008 in Norway. The International Classification of Diseases (ICD) system is used to record diseases and procedures with different versions being used depending on the calendar year and country (Supplementary Table S2). Validation studies of the Nordic patient registries have reported positive predictive values ranging from 75% to 99% for most diagnoses and procedures, and vary dependent on diagnosis, procedure, and country [26–30].

3. *The cancer registries* contain anatomical site, histological cell type, basis of diagnosis, stage, and date of diagnosis for all newly diagnosed malignancies. The national cancer registries started and had mandatory reporting from years 1953 in Norway, 1954 in Iceland, 1958 in Sweden, 1961 in Finland, and 1987 in Denmark [21]. The high completeness (>96%) and data quality of the Nordic cancer registries are well-validated [31–34].

4. *The cause of death registries* contain the date of death with close to 100% completeness and underlying and contributing causes of death with >96% completeness [21]. The cause of death registries use electronic records from years 1951 in Norway, 1952 in Iceland, 1961 in Sweden, 1969 in Finland, and 1970 in Denmark.

5. *The registries of the total population* contain demographic data, including date of birth, death, and migration, ensuring a close to complete and unbiased follow-up of all cohort participants [35].

Inclusion criteria

Patients were included in NordHePEP if they had at least one dispensed HP eradication treatment prescription in adult age (≥18 years) recorded in any of the Nordic drug registries during the study period. HP eradication treatment was identified by the ATC codes for the drugs included in the standard triple treatment (Supplementary Table S3). To avoid inaccurate inclusion of patients prescribed proton pump inhibitors and these antibiotics for other indications, the two antibiotics included in the triple treatment had to be dispensed simultaneously, and the proton pump inhibitor within one month of any of the two antibiotics. The longer time window for the proton pump inhibitor allowed the inclusion of individuals already on proton pump inhibitor therapy when starting HP eradication treatment. PPI use is not uncommon in HP-infected individuals because symptoms of gastritis or peptic ulcer are frequent prior to being diagnosed with HP infection. Each prescription had to cover at least 7 days of treatment duration.

All patients were included in the cohort at the time of their first eradication treatment. Any repeated HP eradication treatment in the same individual was considered to be either due to unsuccessful HP eradication (recrudescence) or a new infection (re-infection), depending on the time elapsed from the previous prescription (Supplementary Figure S1) [36]. If another HP eradication treatment was initiated within 12 months of a previous one, the first treatment(s) was deemed unsuccessful and the date of eradication was set to the date of the last treatment. Individuals with an additional HP eradication treatment prescribed >12 months after a previous treatment were considered to have been re-infected, in which case they were still included at the first eradication, but marked in the cohort in order to enable future sensitivity analyses excluding this group of patients.

Individuals with less than 12 months of follow-up after HP eradication treatment were excluded to ensure complete follow-up for assessment of whether the HP eradication was successful.

Patient recruitment

The enrolment into NordHePEP is described in Figure 1. After identifying a preliminary study population based on our inclusion criteria, we excluded 354 individuals with missing or ambiguous recordings of sex, date of birth, or date of death, as well as 590 individuals with re-used personal identity numbers. The final cohort consisted of 674,771 individuals with HP eradication treatment. National data from each Nordic country were transferred to secured servers at Karolinska Institutet in Sweden or Statistics Denmark, depending on local regulations, for storage, management, and analysis. Before data transfer, all observations were pseudo-anonymised by replacing the personal identity number with an arbitrary serial number. Country-specific cohorts were created by linking the registry data using the arbitrary serial number.

The inclusion of cohort participants by calendar year is presented in Figure 2. The number of included individuals per year in each country reflects the different time intervals of inclusion across countries. Depending on the year of the launch of the national prescribed drug registries, inclusion started first in Denmark and Finland (1994), followed by Iceland (2002), Norway (2004), and Sweden (2005). The final

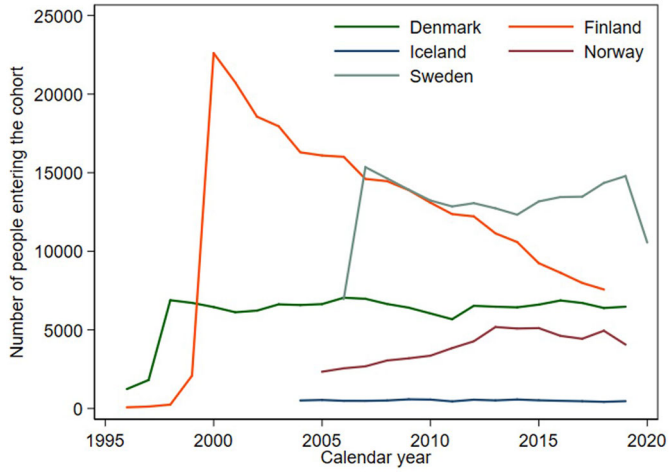

Figure 2. Inclusion of participants having had eradication treatment for Helicobacter pylori infection in any of the five Nordic countries by calendar year and country.

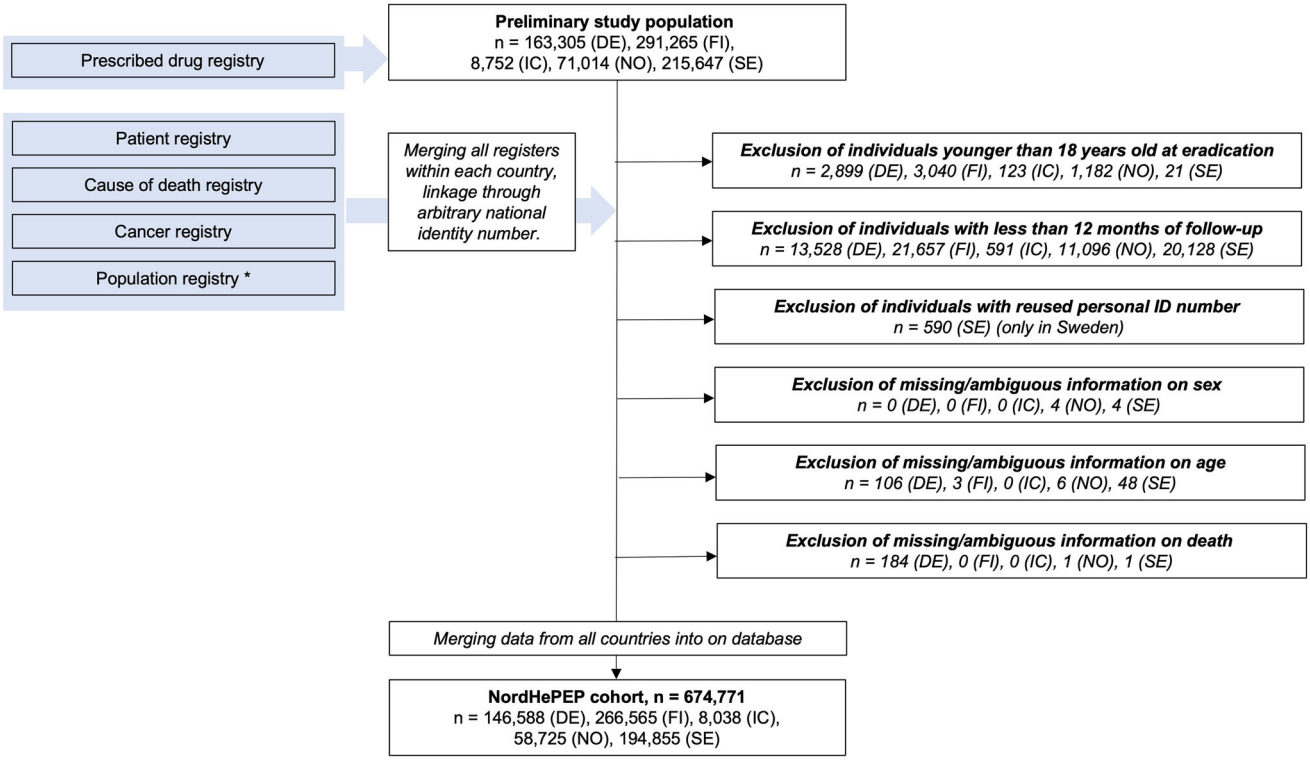

Figure 1. Enrolment of participant having had eradication treatment for Helicobacter pylori infection in any of the five Nordic countries into the cohort. DE: Denmark; FI: Finland; IC: Iceland; NO: Norway; SE: Sweden. *Only in Sweden, Finland and Denmark.

year of inclusion was 2019, except for in Sweden where inclusion continued until mid-2020. In Sweden, data collection started and ended in the middle of a calendar year, explaining the deviating slopes at the beginning and end of study inclusion in Figure 2. In Denmark and Finland, a peak in HP eradication treatment rate coincided with the *Maastricht consensus report* published in 1997, establishing a global approach to HP infection management and eradication [37]. The higher number of prescribed eradication treatments in Finland compared to the other countries reflects a more aggressive HP eradication strategy and a higher prevalence of HP infection in Finland [38]. In the other Nordic countries, the number of HP eradication treatments was fairly stable or slightly increased during the study period, and corresponded to the country's population sizes (Figure 2).

Follow-up

Data collection from each national registry started from the year of nationwide coverage (except for in Finland where the study period was limited due to country-specific regulations) and ended at varying years depending on the date of submission of the data order. Specific dates of data availability in each national registry are presented in Table 1.

In order to avoid detection bias, start of follow-up was set to 12 months after date of the first HP eradication treatment. Participants were followed until date of death, emigration, or end of study period, whichever came first. The maximum length of follow-up was 23 years. Future updates of the cohort will result in even longer follow-up, more updated information on various covariates and outcomes, and inclusion of a larger number of participants.

Measured variables

Main variables collected from each of the five types of registries are summarised in Figure 3, and included information regarding demography, medications, diagnoses (including cancer), surgical procedures, and mortality. Due to data regulations in Iceland and Norway, time for birth, death, and diagnoses were truncated to year and month (not date). For uniformity reasons, these data were truncated similarly for all countries. Date of diagnoses and procedures from inpatient care was set to the date of hospital discharge (or date of hospital admission if missing).

Results

Table 2 presents some baseline characteristics of the cohort participants. The largest number of participants were recruited from Finland (40.2%), followed by Sweden (28.5%), Denmark (21.5%), Norway (8.6%), and Iceland (1.2%). The median age at inclusion was 57 years (interquartile range 43–69 years) and 54.3% were women. Comorbidity was

Table 1. Data availability in the five types of national registries used in each of the five Nordic countries.

		Denmark	Finland	Iceland	Norway	Sweden
Prescribed drug registry		1995 m01-2019 m12	1995 m01-2019 m12	2003 m01-2019 m12	2004 m01-2020 m12	2005 m02-2021 m08
Patient registry		1977 m01-2018 m12	1987 m01-2019 m02	1999 m01-2020 m04	2008 m01-2019 m12	1968 m12-2020 m12
Cancer register		1943 m02-2019 m12	1987 m01-2018 m12	1961 m04-2020 m08	1953 m07-2019 m12	1958 m02-2019 m12
Cause of death registry		1971 m09-2020 m12	1998 m02-2018 m12	2004 m03-2020 m12	2004 m02-2019 m12	1964 m02-2021 m09
Population registry	Birth	1886 m11-2019 m06	1898 m02-2017 m09	1912 m01-2009 m10	ϕ	ϕ
	Immigration	1962 m12-2020 m12	–	2001 m12-2019 m10	–	1912 m07-2020 m12
	Emigration	1969 m05-2020 m12	1995 m08-2021 m03	2000 m01-2019 m12	–	1949 m04-2020 m12

ϕ Data on birth were available from the prescribed drug registry.

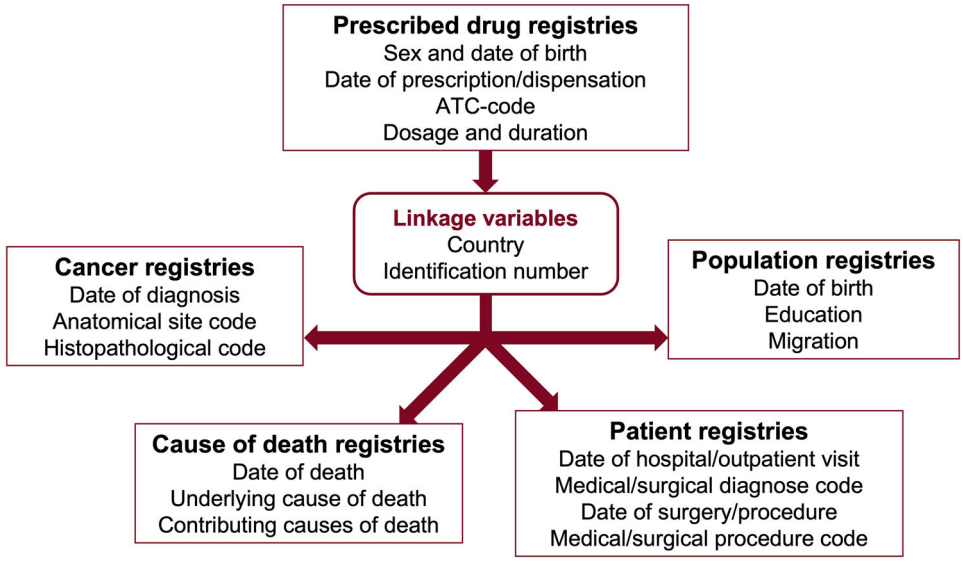

Figure 3. Main variables from the national health data registries included in the cohort from the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden).

assessed using the latest version of the well-validated Charlson comorbidity index for patient registries (Supplementary Table S4) [39]. To reflect the comorbidity burden at the time of cohort entry, we included diagnoses recorded within 5 years of inclusion or set to missing if less than 5 years of data were available in the patient registries. A majority of cohort participants (73.7%) had a Charlson comorbidity index score of 0. Missing data on comorbidity (3.7%) were largely due to the late start of the Norwegian Patient Registry (2008) compared to the Norwegian Drug Registry (2004). The proportions of unsuccessful HP treatment or re-infection with HP were 6.2% and 6.9%, respectively.

Table 3 describes the type of prescribed HP eradication treatment medications used by country. A combination package for HP eradication with the standard triple treatment was only available in Sweden and Finland, where it was the dominating prescription. In the other countries, amoxicillin together with clarithromycin was the most commonly prescribed antibiotic combination in the standard triple treatment.

The follow-up of 674,771 cohort participants for a mean of 8.6 years has provided a total of 5,766,914 person-years after HP eradication treatment. During this follow-up, 59,292 (8.8%) individuals were diagnosed with any cancer (except non-melanoma skin cancer), whereof 15,496 (2.3%) in the gastrointestinal tract. The ICD versions and codes used to categorise the different cancer types are specified in Supplementary Table S5.

Table 2. Characteristics of cohort participants having had eradication treatment for Helicobacter pylori in any of the five Nordic countries.

Variable	Number of participants (%)
Total	674 771 (100.0)
Country (alphabetic order)	
Denmark	146 588 (21.7)
Finland	266 565 (39.5)
Iceland	8 038 (1.2)
Norway	58 725 (8.7)
Sweden	194 855 (28.9)
Sex	
Male	308 555 (45.7)
Female	366 216 (54.3)
Age (years)	
18–30	54 122 (8.0)
31–40	81 769 (12.1)
41–50	111 730 (16.6)
51–60	139 349 (20.7)
61–70	137 909 (20.4)
71–80	104 401 (15.5)
>80	45 491 (6.7)
Calendar period of inclusion (year)	
1996–2000	48 232 (7.1)
2001–2005	125 211 (18.6)
2006–2010	186 725 (27.7)
2011–2015	177 514 (26.3)
2016–2020	137 089 (20.3)
Charlson comorbidity index score	
0	496 885 (73.6)
1	103 526 (15.3)
≥2	49 077 (7.3)
Missing	25 283 (3.7)
Unsuccessful Helicobacter pylori eradication	42 121 (6.2)
Re-infection with Helicobacter pylori	46 703 (6.9)

Discussion

In this cohort profile paper we describe the construction of NordHePEP and characteristics of the cohort participants. It shows it is possible to retrieve and merge data, including drug use, from all Nordic countries to create large and population-based cohorts.

Among strengths of NordHePEP is the large number of participants having had HP eradication treatment and the long and complete follow-up. This enables subgroup analyses, and assessment of outcomes with a low incidence and a long latency period, e.g., cancer. The population-based design minimises the risk of selection bias and reflects real-world clinical practice, facilitating representativeness and generalisability. The similarly structured national health data registries in the Nordic countries, containing relevant data with high completeness and quality, allowed for merging of extensive amounts of individual data. The key to linkage of individuals data was the personal identity number system used in all Nordic countries. The linkage of data through the identity numbers will also enable future updates with additional participants, data, and length of follow-up. The complete and accurate cancer incidence data for the entire populations in the five Nordic countries make it possible to use the corresponding background population as a comparison group and calculate standardised incidence ratios. These strengths provide opportunities for valid studies examining associations between HP eradication treatment and various outcomes, including cancer.

Limitations include that fact that there are no participants unexposed to Helicobacter pylori treatment within the cohort. Thus, external unexposed cohorts are required for comparison. There is some uncertainty regarding patient compliance to the HP eradication treatment. However, cohort inclusion criteria required not only prescription but also dispensation of HP eradication medications, which means out-of-pocket payment and improved compliance. The clinical

Table 3. Distribution of Helicobacter pylori eradication treatment regimens used for inclusion in the cohort from the five Nordic countries, presented as numbers (%).

Country	PPI[a] + amoxicillin and clarithromycin	PPI[a] + metronidazole and clarithromycin	PPI[a] + amoxicillin and metronidazole	Combination package
All	268 904 (34.1)	5 568 (0.7)	25 607 (3.3)	488 629 (61.9)
Denmark	158 283 (91.6)	2 963 (1.7)	11 563 (6.7)	- (0.0)
Finland	19 262 (6.0)	38 (0.0)	308 (0.1)	297 234 (93.8)
Iceland	8 621 (99.0)	28 (0.3)	54 (0.6)	- (0.0)
Norway	51 922 (78.6)	1 957 (3.0)	12 139 (18.4)	- (0.0)
Sweden	30 816 (13.7)	582 (0.3)	1 543 (0.7)	191 395 (85.3)

[a]Proton pump inhibitor.

guidelines in the Nordic countries state the need to perform a control test (mainly F-Hb) minimum 4 weeks after completed HP eradication treatment, and additional eradication treatment if this test shows remaining infection. However, there remains some uncertainty to what degree the HP eradication was successful or not in this cohort because information on post-eradication assessments was not available. Therefore, our definition of 'successful eradication' (no additional recorded treatments 12 months after eradication) is an estimation and may include some patients who were not eradicated, e.g., those who were asymptomatic after treatment and therefore did not seek additional healthcare. The eradication failure rate of 6.2% is thus likely an underestimation. Therefore, the cohort may be used for future studies examining effects of HP *eradication treatment* rather than proven HP *eradication*. Individuals defined as re-infected with HP in the cohort were still included at the first eradication. Since we do not know exactly when they were re-infected, this group may introduce bias in future studies examining cancer incidence. Thus, we have marked this group in the cohort to enable sensitivity analyses excluding these patients. It is possible that some cohort participants were eradicated before the study period and re-infected prior to their first recorded eradication treatment in the cohort. However, this should be a small group and should not much affect the results.

The standard triple treatment is the recommended 1st and 2nd line of treatment in the Nordic countries. In a study evaluating different regimens for eradication treatment in Sweden, only 5% of prescriptions differed from the standard recommendation [40]. To avoid misclassification of HP eradication treatment, only the drugs included in the standard triple treatment were included in this cohort. The drug registries lack complete details on the indications for medication use which connotes a risk of exposure misclassification. The time for drug dispensation was limited to month and year in our data, not exact dates, why drugs prescribed on the same month and year were assumed to be dispensed simultaneously. This could potentially introduce some level of exposure misclassification. However, we have made efforts to circumvent these issues by applying well-informed and strict definitions of HP eradication treatment, unsuccessful treatment, and re-infection (Supplementary Figure S1). Finally, data were missing or less detailed for some covariates, e.g., lifestyle and dietary factors.

Ethical approvals and permissions

Ethical approvals were obtained from the relevant scientific ethical authorities in Iceland, Norway, and Sweden (permissions VSN 19-181, REK-32617, and 2019-04473, respectively), while ethical approval was not required in Denmark or Finland. Additional permissions were acquired from the data protection authorities in Denmark and Iceland; the registry holders in Finland, i.e., the Social Insurance Institution of Finland (prescribed drug registry, permission 122/522/2019), National Institute for Health and Welfare (patient and cancer registry, permission THL/1732/5.05.00/2019), Statistics Finland (education and cause of death registry, permission TK-53-1429-19) and Digital and Population Data Services Agency in Finland (emigration registry, permission DVV/7561/2020-1); the registry holders in Norway i.e., the Institute of Public Health (20/11049), the Norwegian Directorate of Health (20/10502) together with a Data Protection Impact Assessment (DPIA) and a Data Processor Agreement with Karolinska Institutet; and the registry holders in Sweden, i.e., the National Board of Health and Welfare and Statistics Sweden (38587/2019).

Author contributions

JL came up with the idea of this cohort. MvEC (Denmark), JK (Finland), HB (Iceland), ENJ (Norway), and JL and SX (Sweden) handled the permissions and data collection within each country. AKP, JY, and GS did the management, cleaning and merging of data and the analyses. AKP drafted the manuscript. All authors revised the manuscript. JL is responsible for the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Anna-Klara Pettersson http://orcid.org/0000-0003-0974-3284
Eivind Ness-Jensen http://orcid.org/0000-0001-6005-0729
Joonas H. Kauppila http://orcid.org/0000-0001-6740-3726

Data availability statement

NordHePEP data can be shared for research purposes upon request by contacting the Chief Investigator, Professor Jesper Lagergren, but may be restricted by and require complimentary permissions from the relevant ethical committees and original data holders.

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