# Long term use of proton pump inhibitors and risk of stomach cancer: population based case-control study in five Nordic countries

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## ABSTRACT

### OBJECTIVE

To help to clarify whether long term use of proton pump inhibitors is associated with an increased risk of gastric adenocarcinoma by designing a study that considered the existing literature's methodological weaknesses.

### DESIGN

Population based case-control study using prospectively collected data from multiple complete nationwide registries in five Nordic nations.

### SETTING

All healthcare in five Nordic countries—Denmark, Finland, Iceland, Norway, and Sweden—between 1994 and 2000.

### PARTICIPANTS

Case patients with gastric adenocarcinoma, each matched for age, sex, calendar year, and country with 10 control participants randomly identified from each country's entire population.

### EXPOSURE

The exposure was long term (>1 year) proton pump inhibitor use, excluding the 12 months before the diagnosis date (cases) or inclusion date (controls). Long term (>1 year) use of histamine-2-receptor antagonists was analysed to assess the validity and specificity of the findings for proton pump inhibitor use

### MAIN OUTCOMES MEASURES

The outcome was gastric non-cardia adenocarcinoma. Gastric cardia adenocarcinoma was excluded to avoid confounding by indication (that is, gastro-oesophageal reflux). As well as controlling for the matching variables, multivariable logistic regression provided odds ratios with 95% confidence intervals, adjusted for country, *Helicobacter pylori* treatment, peptic ulcer disease, smoking related diseases, alcohol related diseases, obesity or type 2 diabetes, and drug treatment with metformin, non-steroidal anti-inflammatory drugs, and statins.

### RESULTS

The study included 17 232 cases of gastric (non-cardia) adenocarcinoma and 172 297 controls. Long term proton pump inhibitor use occurred in 1766 (10.2%) cases and 16 312 (9.5%) controls. No association was found between long term proton pump inhibitor use and gastric adenocarcinoma (adjusted odds 1.01, 95% confidence interval 0.96 to 1.07). The risk was similar for histamine-2-receptor antagonist use (adjusted odds ratio 1.03, 0.86 to 1.23). Multiple sources of error that led to a false positive association were identified—inclusion of proton pump inhibitor use shortly before the gastric adenocarcinoma diagnosis, short term use of proton pump inhibitors, cardia adenocarcinoma, and lack of adjustment for *Helicobacter pylori* related variables.

### CONCLUSIONS

Long term proton pump inhibitor use may not be associated with an increased risk of gastric adenocarcinoma.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

A fear that proton pump inhibitor therapy could lead to gastric cancer has been ongoing since the 1980s when these drugs entered the market

Three recent meta-analyses show an approximately twofold increase in the risk of gastric cancer with proton pump inhibitor use

However, the literature is hampered by several methodological limitations, making this possible association uncertain

## WHAT THIS STUDY ADDS

This multinational and population based study made extensive efforts to avoid and assess all the methodological limitations hampering the existing literature

After the limitations were managed, the results show no remaining association between long term proton pump inhibitor use and risk of gastric adenocarcinoma

This finding should offer relief for patients needing long term proton pump inhibitor therapy and is valuable for clinical decision making in healthcare settings

## Introduction

Gastric cancer is the fifth most common malignancy globally.[1] The dominating histology is adenocarcinoma (>95%). Rarer gastric malignancies, such as neuroendocrine tumours, gastrointestinal stromal tumours, and lymphomas, have different aetiology and treatment. *Helicobacter pylori* infection is the main risk factor for gastric adenocarcinoma distal to the cardia, and gastro-oesophageal reflux disease is the major risk factor for cardia adenocarcinoma.[2]

The main indication for long term use of proton pump inhibitors is gastro-oesophageal reflux disease, which has a prevalence of 15-20% among adults in western populations.[3] Long term usage of proton pump inhibitors has been proposed as a risk factor for gastric cancer since their introduction in the 1980s.[4] The proposed mechanism is a compensatory overproduction of the enzyme gastrin (hypergastrinaemia), which stimulates parietal and enterochromaffin-like cells in the gastric mucosa distal to the cardia to secrete acid.[5] The resultant hyperproliferation of these cell types can lead to gastric polyps, some of which contain cells that may have the potential for malignant transformation.[6 7]

Many studies that have assessed proton pump inhibitor use and risk of gastric cancer have reported an increased risk.[8-10] A recent systematic review on the topic concluded that although the literature suggests a positive association between proton pump inhibitor use and gastric cancer, the studies are hampered by major methodological limitations, such as low statistical power, short and incomplete follow-up, inclusion of proton pump inhibitor exposure shortly before the gastric cancer was diagnosed (protopathic bias), differences in classification of cases (methodological heterogeneity), and inability to adjust for *Helicobacter pylori* infection and other relevant confounders.[11] Therefore, whether long term proton pump inhibitor use increases the risk of gastric adenocarcinoma remains uncertain.

Conducting a randomised controlled trial to examine this research question is not feasible, so instead we aimed to conduct an observational study that was designed to consider all the main limitations of the existing literature, the aim of which was to clarify whether long term use of proton pump inhibitors is associated with an increased risk of gastric adenocarcinoma.

## Methods

### Design

This was a multinational and population based case-control study between 1994 and 2020, called the Nordic Gastric and Esophageal Tumor Study (NordGETS). The NordGETS includes all patients with gastric (and oesophageal) cancer and 10 times as many population control participants from all five Nordic nations—Denmark, Finland, Iceland, Norway, and Sweden (alphabetical order). Data came from five different registries in each of these countries: the registries of the total population, prescribed drugs, cancer, all diagnoses, and death. These registries are all complete nationwide and are similar between the countries, and the data have high quality, completeness, and congruence.[12] Within the study period, the start year varied depending on the initiation of the prescribed drug registries in the participating countries—1994 in Denmark and Finland, followed by Iceland and Norway (2003), and Sweden (2005).

### Data sources

The registries of the total population contain 100% complete information on demographic variables for all residents.[12] The information is continuously updated, allowing us to obtain data on new events within a few weeks of their occurrence. We identified the control participants for this study from these registries and obtained information on sex, age, country, and emigration.

The prescribed drug registries contain data on all prescribed and dispensed drugs. The information is electronically and automatically submitted from the pharmacies to the drug registries, which is encouraged by financial and legal incentives.[12 13] These registries provide information on both prescription and dispensation of the relevant drugs; for this study, we considered only dispensed drugs to avoid including non-use.

The cancer registries include information on all malignancies with at least 96% coverage overall, and 98% for gastric adenocarcinoma, as evidenced by large validation studies.[14 15] The data have consistently been shown to be of high quality and completeness.[16] For this study, these registries provided information on all gastric adenocarcinoma diagnoses, including date of diagnosis and tumour sublocation.

The patient registries contain data on all diagnoses and surgical procedures from in-hospital care and specialised outpatient care. Validation studies have shown positive predictive values ranging from 73% to >90%.[17-20] These registries provided information on diseases and conditions that we included as covariates in this study.

The cause of death registries have 100% complete information on date of death,[21] which we used for censoring purposes in the study.

All the registries above contain personal identity numbers, which are 10-11 digit codes assigned to every resident of the Nordic countries.[12] These numbers enabled exact linkages of registry data for each study participant. No missing data were reported in the registries.

### Participants

We included as cases all patients with a diagnosis of gastric (non-cardia) adenocarcinoma in any of the national cancer registries occurring one year or later after the start of the national drug registry. We did not include histological types of gastric malignancies other than adenocarcinoma to avoid misclassification of the outcome. For each case, we randomly identified 10 controls without a history of gastro-oesophageal cancer from the entire general population (the registries of the total population) of the five countries and matched them for age, sex, calendar year, and country at the index date. We defined the index date as the date of diagnosis of gastric adenocarcinoma for the cases and the date of matching for the controls, equalling the date of diagnosis for the respective case. We included only participants with a possibility of having at least five years of medication history in the drug registries to ensure the same amount of exposure time for all cases and controls.

### Exposure

The exposure was long term use of a proton pump inhibitor of any formulation. Because the mechanism of action and thus the hypothesised carcinogenic pathways are the same for the different types of proton pump inhibitor, we did not analyse different types separately. We considered dispensations of proton pump inhibitors during the five years before inclusion but disregarded exposure within 12 months before the index date to avoid confounding by any symptomatic but undiagnosed gastric adenocarcinoma. We calculated the defined daily doses of proton pump

inhibitor cumulatively, using the final value to assess the duration of proton pump inhibitor use. We defined long term use as more than one year. This cut-off is commonly used and is supported by studies that have shown that lesions associated with proton pump inhibitor use, such as fundic gland polyps, start to occur after one year of use.[22] Proton pump inhibitors can be used continuously or intermittently. We considered intermittent use as exposure if the cumulative defined daily doses corresponded to more than one year of use. This was motivated by the persistence of hypergastrinemia even after temporary withdrawal of proton pump inhibitor.[23] We included long term (more than one year) use of a histamine-2-receptor antagonist as a comparator exposure to assess whether the findings for proton pump inhibitor use were specific to this drug type and to evaluate the validity of the findings for proton pump inhibitor use. Histamine-2-receptor antagonists are mainly used for the same indications as proton pump inhibitors and are not associated with gastric adenocarcinoma.[24 25] We defined exposure to histamine-2-receptor antagonists in the same way as for proton pump inhibitors.

### Outcome

The outcome was gastric non-cardia adenocarcinoma. We excluded cardia adenocarcinoma because cardia does not contain the cells that are supposed to be involved in proton pump inhibitor driven carcinogenesis and to avoid confounding by indication because of its strong association with gastro-oesophageal reflux disease, which is the main indication for long term proton pump inhibitor treatment.[3] We excluded histological types of gastric tumours other than adenocarcinoma because of major differences in aetiology.[26]

### Covariates

We considered 12 covariates to be potential confounders because they may increase or decrease the risk of development of gastric cancer. We considered nine covariates as potential risk factors: age (continuous), sex (male or female), calendar year (continuous), country (Denmark, Finland, Iceland, Norway, or Sweden), *Helicobacter pylori* eradication treatment (no or yes, at least 12 months before the index date), peptic ulcer disease (no or yes, at least 12 months before the index date), smoking related diseases, alcohol related diseases, and obesity or type 2 diabetes (no or yes).[26] We included three covariates because they may decrease the risk: at least six months' use of the medications metformin (no or yes), non-steroidal anti-inflammatory drugs (no or yes), and statins (no or yes), as these can be considered as protective.[26 27]

### Statistical analysis

We used conditional logistic regression to calculate odds ratios with 95% confidence intervals. The reference group had no exposure (no or less than one month of use), and the exposed group had at least one year of use. In a crude model, we controlled for the covariates sex, age, calendar year, and country by incorporating the group variable for the matched pairs as strata. In a multivariable model, we additionally made adjustments for all eight remaining covariates with the categorisations described above. We did the same analyses for histamine-2-receptor antagonist use. The analyses followed a pre-defined study protocol.

As well as examining histamine-2-receptor antagonist use for evaluating biased results, we added analyses to assess whether four of the measures undertaken to avoid bias were relevant. Firstly, we shortened the length of the disregarded exposure time before the index date from 12 months to six months and calculated the yearly odds ratios of heavy proton pump inhibitor use (≥365 defined daily doses) and of receiving a diagnosis of dyspepsia before the index date. Secondly, we examined short term proton pump inhibitor use—that is, between more than one month and up to one year. Thirdly, we included cardia adenocarcinoma. Fourthly, we excluded the covariates *Helicobacter pylori* eradication and peptic ulcer from the multivariable model.

An experienced biostatistician (GS) was responsible for the data management and statistical analyses, using the statistical software Stata (version X MP 18.0).

### Patient and public involvement

We discussed the study with a patient partnership group consisting of eight to 12 patients who had undergone treatment for oesophageal or gastric cancer, who we meet four times each year to discuss new studies. We discussed this study with the patient group, and they gave it their full support and did not suggest any changes to the original study protocol.

## Results

### Participants

The study included 17 232 cases with gastric (non-cardia) adenocarcinoma and 172 297 controls. The distribution of risk factors was as expected, with *Helicobacter pylori* related variables (eradication treatment and peptic ulcer disease), smoking related disorders, and obesity being more common among the cases than the controls (table 1).

### Proton pump inhibitors and gastric adenocarcinoma

During the study period for up to 26 years, long term use of proton pump inhibitors was not associated with any increased risk of gastric (non-cardia) adenocarcinoma (adjusted odds ratio 1.01, 95% confidence interval (CI) 0.96 to 1.07) (table 2). The crude odds ratio was increased (1.16, 95% CI 1.10 to 1.23), but adjustment for confounders, especially *Helicobacter pylori* related variables, removed the association.

### Histamin-2-receptor antagonists and gastric adenocarcinoma

Long term histamine-2-receptor antagonist users showed no increased risk of gastric (non-cardia)

**Table 1 | Characteristics of gastric (non-cardia) adenocarcinoma cases and population controls. Values are numbers (percentages) unless stated otherwise**

| Characteristics | Cases (17 232) | Controls (172 297) |
|---|---|---|
| Sex: | | |
| Female | 7309 (42.4) | 73 084 (42.4) |
| Male | 9923 (57.6) | 99 213 (57.6) |
| Median (IQR) age, years | 74 (65-81) | 74 (65-81) |
| Median (IQR) calendar year | 2012 (2007-2016) | 2012 (2007-2016) |
| Country: | | |
| Denmark | 4098 (23.8) | 40 970 (23.8) |
| Finland | 5593 (32.5) | 55 930 (32.5) |
| Iceland | 202 (1.2) | 2020 (1.2) |
| Norway | 2402 (13.9) | 23 997 (13.9) |
| Sweden | 4938 (28.7) | 49 380 (28.7) |
| PPI use—mean (SD) DDDs | 132.2 (388.6) | 120.4 (378.3) |
| H2RA use—mean (SD) DDDs | 10.3 (104.8) | 8.2 (80.6) |
| Covariates: | | |
| *Helicobacter pylori* | 538 (3.1) | 2275 (1.3) |
| Peptic ulcer | 1668 (9.7) | 11 008 (6.4) |
| Smoking related disorders | 1429 (8.3) | 9917 (5.8) |
| Alcohol related disorders | 651 (3.8) | 4863 (2.8) |
| Obesity | 2169 (12.6) | 16 142 (9.4) |
| Metformin use* | 1821 (10.6) | 14 940 (8.7) |
| NSAID use* | 6711 (38.9) | 68 047 (39.5) |
| Statin use* | 5417 (31.4) | 54 307 (31.5) |
| Median (IQR) follow-up, years | 5.0 (5.0-5.0) | 5.0 (5.0-5.0) |

DDD=defined daily dose; H2RA=histamine 2-receptor antagonist; IQR=interquartile range; NSAID=non-steroidal anti-inflammatory drug; PPI=proton pump inhibitor; SD=standard deviation.
*At least 180 defined daily doses.

adenocarcinoma (adjusted odds ratio 1.03, 95% CI 0.86 to 1.23) (table 3). The crude estimate was increased (odds ratio 1.14, 95% CI 0.96 to 1.36), but it did not remain so after adjustment for confounders.

### Assessment of sources of bias

The use of a six month dismissal period instead of 12 months for proton pump inhibitor use before the index date rendered an increased risk of gastric (non-cardia) adenocarcinoma (odds ratio 1.11, 95% CI 1.06 to 1.16) (supplementary table A). The adjusted odds ratios of proton pump inhibitor use and dyspepsia were clearly increased during the 12 months preceding the index date (supplementary figure A).

Short term proton pump inhibitor use was associated with an increased risk of gastric (non-cardia) adenocarcinoma (adjusted odds ratio 1.32, 95% CI 1.26 to 1.39) (supplementary table B), which we also found for short term histamine-2-receptor antagonist use (1.20, 1.07 to 1.34) (supplementary table B). When we combined short term and long term proton pump inhibitor users into an "ever user" category, the risk was also increased (adjusted odds ratio 1.18, 95% CI 1.13 to 1.23) (supplementary table C).

Long term proton pump inhibitor users had an increased risk of gastric adenocarcinoma when we included cardia adenocarcinoma (adjusted odds ratio 1.13, 95% CI 1.08 to 1.18), and we found a similar association for long term histamine-2-receptor antagonist use in such a combined analysis (1.14, 0.99 to 1.32) (supplementary table D).

After exclusion of the covariates *Helicobacter pylori* eradication and peptic ulcer from the multivariable model, the risk of gastric (non-cardia) adenocarcinoma became increased among long term proton pump inhibitor users (partially adjusted odds ratio 1.11, 95% CI 1.05 to 1.17) and long term histamine-2-receptor antagonist users (1.10, 0.92 to 1.31) (supplementary table E).

## Discussion

The results of this study do not support the hypothesis that long term use of proton pump inhibitors is associated with an increased risk of gastric adenocarcinoma. Every one of the various steps used to prevent biases was essential to prevent the reporting of a potentially false association.

**Table 2 | Use of proton pump inhibitors and risk of gastric (non-cardia) adenocarcinoma. Values are numbers (percentages) unless stated otherwise**

| Proton pump inhibitor use | Cases | Controls | Crude odds ratio (95% CI)* | Adjusted odds ratio (95% CI)*† |
|---|---|---|---|---|
| None (≤1 month) | 13 077 (75.9) | 138 652 (80.5) | 1.00 (reference) | 1.00 (reference) |
| Long term (>1 year) | 1766 (10.2) | 16 312 (9.5) | 1.16 (1.10 to 1.23) | 1.01 (0.96 to 1.07) |

CI=confidence interval.
* Matched for sex, age, calendar year, and country.
† Adjusted for *Helicobacter pylori* treatment, peptic ulcer, smoking related disorders, alcohol related disorders, obesity or diabetes type 2, and long term use of metformin, non-steroidal anti-inflammatory drugs, and statins.

**Table 3 | Use of histamine-2-receptor antagonists and risk of gastric (non-cardia) adenocarcinoma. Values are numbers (percentages) unless stated otherwise**

| H2RA use | Cases | Controls | Crude odds ratio (95% CI)* | Adjusted odds ratio (95% CI)*† |
|---|---|---|---|---|
| None (≤1 month) | 16 736 (97.1) | 168 368 (97.7) | 1.00 (reference) | 1.00 (reference) |
| Long term (>1 year) | 139 (0.8) | 1230 (0.7) | 1.14 (0.96 to 1.36) | 1.03 (0.86 to 1.23) |

CI=confidence interval; H2RA=histamine-2-receptor antagonist.
*Matched for sex, age, calendar year, and country.
†Adjusted for *Helicobacter pylori* treatment, peptic ulcer, smoking related disorders, alcohol related disorders, obesity or diabetes type 2, and long term use of metformin, non-steroidal anti-inflammatory drugs, and statins.

### Strengths and limitations of this study

Among methodological strengths is the population based design with complete participation, counteracting selection bias. The multinational approach enabled risk estimates of high precision. The registry data on the exposures, outcome, and covariates were prospectively collected and of high quality and completeness. The long study period (up to 26 years) and complete follow-up made assessment of cancer risk possible and enabled us to mitigate the problem of latency bias. Inclusion of only adenocarcinoma histology reduced misclassification. Confounding was counteracted by exclusion of cardia adenocarcinoma, dismissal of proton pump inhibitor exposure 12 months before index date, assessment of long term (more than one year) exposure to proton pump inhibitor use, and adjustment for the main risk factors, including *Helicobacter pylori* infection related covariates. The results from the analyses of histamine-2-receptor antagonists support the validity of the findings for proton pump inhibitor use. Generalisability is facilitated by the population based and multinational design.

Among weaknesses is that the case-control design might be prone to recall bias and selection bias. However, the data in this study were prospectively collected in registries, which prohibited recall bias, and the population based design with complete inclusion of participants avoided selection bias. The case-control approach maximised the statistical power because all cases in five countries were identified. This would not have been possible using a cohort design because it would require inclusion of all individuals in the five countries and extensive data on all, which is neither allowed nor feasible. Instead, the case-control design allowed us to retrieve information about all variables for a large sample of the general populations—that is, the controls. Confounding is a major concern in most observational studies, and confounding by indication is a special threat to the validity of investigations examining drug treatment. We made extensive efforts to avoid confounding, but a few risk factors were not accounted for. We did not have information about dietary factors, including salt intake. However, salt intake may not be a strong risk factor in western populations.[28 29] The risk factors family history of gastric cancer, previous surgery for benign gastric conditions, and Zollinger-Ellison syndrome were too rare to be included in the models or influence the results. Furthermore, we cannot think of any confounder that could cause the study's findings of a lack of an association between long term proton pump inhibitor usage and the risk of gastric adenocarcinoma to be false.

### Comparison with other studies

Most previous studies have shown an increased risk of gastric cancer among proton pump inhibitor users. Three recent systematic reviews and meta-analyses on the topic have reported pooled relative risk estimates of 2.88 (95% CI 2.29 to 3.61), 1.75 (1.28 to 2.40), and 1.67 (1.39 to 2.00).[8-10] The methodological limitations highlighted in this study, such as the absence of a sufficiently long dismissal period of the exposure before the diagnosis of cancer, the assessment of short term proton pump inhibitor exposure, the inability to exclude cardia adenocarcinoma, and the inability to account for *Helicobacter pylori* infection and other confounders, may be the cause of the positive association noted in most of the earlier literature. By doing additional analyses to assess biases, this study overcame each of these limitations and provided possible methodological explanations for the discrepancies in results. The inclusion of proton pump inhibitor use shortly before the diagnosis of gastric cancer resulted in an association, likely due to symptoms of the unidentified gastric cancer. The inclusion of short term proton pump inhibitor use increased the risk estimates, which was probably explained by the fact that short term proton pump inhibitor therapy is often used for *Helicobacter pylori* associated conditions, mainly ulcers, again resulting in confounding by indication. This interpretation is supported by similar findings for histamine-2-receptor antagonist use. The inclusion of cardia adenocarcinoma led to an association, highlighting introduction of confounding by indication (that is, gastro-oesophageal reflux disease), which is both an indication for proton pump inhibitor use and a risk factor for cardia adenocarcinoma. This interpretation also gains support from the similar results for histamine-2-receptor antagonist use. The adjustment for confounders linked with *Helicobacter pylori* infection was a key factor in the multivariable model. *Helicobacter pylori* infection and eradication treatment influences the need for long term proton pump inhibitor use and the risk of gastric non-cardia adenocarcinoma.[30] Although the absolute contribution from each of the individual highlighted biases towards a false positive association was moderate, they were not negligible and were statistically significant. The cumulative effect of the biases made the difference stronger and in line with the

average association reported in the existing literature. Thus, without avoiding these biases, a clearly false positive association would have been reported.

Gastric atrophy is the main precursor condition of gastric adenocarcinoma, typically caused by *Helicobacter pylori* infection. Long term proton pump inhibitor use is not associated with such atrophy[31]; long term proton pump inhibitor use instead causes hypergastrinaemia, which might lead to hyperproliferation of the gastric mucosa and has been a suggested mechanism for the development of gastric cancer.[32] This has been reported in some animal studies but has not been found in humans.[33] By contrast, a recent study showed that the hallmark gastric mucosal changes associated with long term proton pump inhibitor use—that is, the development of fundic gland polyps or cobblestone-like mucosa—did not show any potential for malignant transformation.[34] Thus, the lack of an association between long term proton pump inhibitor use and gastric adenocarcinoma in this study is supported by the absence of strong mechanistic evidence to suggest that proton pump inhibitor use leads to any development of precancerous or cancerous lesions of the gastric mucosa.

## Policy implications

The finding of no association may offer relief for patients who need long term proton pump inhibitor therapy in the treatment of gastro-oesophageal reflux disease or for other clear indications. This knowledge is also of value for clinical decision making in healthcare settings. However, long term proton pump inhibitor use might cause side effects and increase the risk of some other potentially serious conditions such as *Clostridium difficile* associated diarrhoea, osteoporosis, and vitamin or electrolyte malabsorption,[35] highlighting the need to balance the benefits and disadvantages of such use and to regularly reassess the need for continued proton pump inhibitor treatment.[3]

## Conclusions

This multinational and population based study, in which we made extensive efforts to avoid and assess the methodological problems in the existing literature, indicates that long term proton pump inhibitor use may not be associated with any increased risk of developing gastric non-cardia adenocarcinoma.

**Contributors:** OD contributed to the conceptualisation, data curation, formal analysis, methodology, and validation and wrote the original draft. GS contributed to the conceptualisation, data curation, formal analysis, methodology, validation, and visualisation and reviewed and edited the manuscript. DH contributed to the conceptualisation and methodology and reviewed and edited the manuscript. HB, JHK, MvEC, and ENJ contributed to the conceptualisation, methodology, and resources and reviewed and edited the manuscript. JL was responsible for the conceptualisation, methodology, resources, funding acquisition, and writing of the original draft and reviewed and edited the manuscript. GS, OD, and JL directly accessed and verified the underlying data reported in the manuscript. JL and GS are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Transparency declaration:** The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

**Dissemination to participants and related patient and public communities:** The results of the study will be sent to research participants and the relevant patient organisations.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

**Ethical approval:** The study was approved by all relevant ethical boards (Ethical Review Board in Norway, 32617; Iceland, VSN-19-181; and Sweden, 2019-04473; such approval was not required in Denmark or Finland), data inspectorates, and governmental agencies holding the registries in the participating countries.

**Data sharing:** Restrictions apply to the availability of the data, which were used under licence and are thus not publicly available. Approvals are required from the relevant authorities. Contact the corresponding author for further information.



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**Web appendix:** Supplementary tables and figure