UiT The Arctic University of Norway

Department of Research, Cancer Registry of Norway

Association between the use of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists and the risk of gastric cancer in Norway

A population-based study in Norway

Kenny Khang Tran

Master's thesis in pharmacy May 2021

Foreword

This master´s thesis was written at the Department of Research, Cancer Registry of Norway from August 2020 to May 2021 in Oslo.

I would like to thank my supervisor Bettina Kulle Andreassen for letting me write this master´s thesis at the Cancer Registry of Norway. Without her, this would not have been possible. However, I must acknowledge that writing this master´s thesis mainly from home office has been challenging due to COVID-19. Although it has been challenging, I have learned a lot within the epidemiology field throughout this year. This would not have been possible without my supervisor´s guidance, constructive feedback and support during this research. That is why I sincerely want to express my gratitude for her.

I would also like to honor and dedicate this master´s thesis to my beloved mother. She is the main reason I chose to write this master´s thesis within the cancer field. Unfortunately, she passed away from cancer 11 years ago. She will never be forgotten.

Le Thi Thanh Thuy

(24.01.1972 – 07.11.2009)

Oslo, May 2021

Kenny Khang Tran

Abstract

Background

The use of proton pump inhibitors (PPIs) on prescription has increased over the last decade in Norway. PPIs are an important medication in the treatment of acid related disorders such as peptic ulcer disease, gastroesophageal reflux disease and *Helicobacter Pylori* (*H. Pylori*) infection. However, many previous studies have raised concern about the potential risk of gastric cancer following the use of PPIs. In this registry-based study we will investigate the association between use of PPI and Histamine-2 receptor antagonist (H2RA) and the risk of gastric cancer in Norway.

Methods

This population-based nested case-control study comprises all primary gastric cancer cases in Norway diagnosed between 2007 and 2015 at an age of 18-85 and registered in the Cancer Registry of Norway. Ten cancer free controls were matched to each case on birth year, sex and index date (date of diagnosis). PPI and H2RA drug exposure were retrieved from the Norwegian Prescription Database and modelled as binary use, long-term use, cumulative use and in an active comparator design. Moreover, we used a stratified cox regression adjusted for *H. Pylori*, residency, education, comorbidity and other drug use to assess the link between PPI and H2RA use and the risk of gastric cancer.

Results

Among 33 847 individuals in this study, we found an increased risk of gastric cancer among PPI users (HR=1.25, 95% Cl 1.13-1.37) and long-term PPI users (HR=1.18, 95% Cl 1.03-1.36) in Norway. There was also a significant impact on gastric cancer among PPI users living in Northern Norway (HR=1.43, 95% Cl 1.27-1.61). However, the dose-response relationship for PPI and the corresponding results for H2RA were not associated with an increased risk of gastric cancer. In addition, there was no significant risk of gastric cancer when comparing PPI use directly to H2RA use in an active comparator design (HR=0.98, 95% Cl 0.79-1.21).

Conclusion

The association found between PPI use and the increased risk of gastric cancer was most likely due to confounding by indication like *H. Pylori* infection and other unobserved confounders. Observational studies adjusted for all relevant confounders and larger clinical studies with a longer follow-up are needed to establish or rule out a causal relationship between PPI use and gastric cancer risk in the future.

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Abbreviation List

ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
Cl	Confidence Interval
CRN	Cancer Registry of Norway
DDD	Defined Daily Dose
ECL	Enterochromaffin-like
GERD	Gastroesophageal Reflux Disease
H. Pylori	Helicobacter Pylori
H2RA	Histamine-2 Receptor Antagonist
HR	Hazard Ratio
IQR	Interquartile Range
IRR	Incidence Rate Ratio
NET	Neuroendocrine Tumor
NorPD	Norwegian Prescription Database
NPR	National Patient Register
NSAID	Non-steroidal Anti-inflammatory Drug
OR	Odds Ratio
PPI	Proton Pump Inhibitor
PRI	Patient Registry Index
PUD	Peptic Ulcer Disease

RCT	Randomized Controlled Trials
SIR	Standardized Incidence Ratio
SSB	Statistics Norway

1 Introduction

In 2020, approximately 10% of the Norwegian population received proton pump inhibitor (PPI) on prescription at least once (1). Several previous studies have reported that use of PPIs is associated with an increased risk of gastric cancer, while previous findings on the use of Histamine-2 receptor antagonist (H2RA) and gastric cancer risk has been inconsistent. This population-based nested case-control study is aimed to find the association between use of PPI and H2RA and the risk of gastric cancer in Norway.

1.1 Gastric cancer

Gastric cancer is a malignant tumor that develops from the lining of the stomach and is categorized as C16 according to the International Classification of Disease Tenth Revision (2). Gastric cancer occurs mainly in elderly whereas men are twice as likely to develop gastric cancer compared to women. In addition, 95% of all gastric cancers are adenocarcinomas (3). Gastric cancer is the sixth most common cancer and the fourth cause of cancer-related mortality in the world (4).

In 2019, 440 individuals were diagnosed with gastric cancer (C16) in Norway, with 279 of them being men while 161 were women. The median age of gastric cancer diagnosis was 73, and there was twice as many gastric cancer cases in men compared to women. Hordaland followed by Trøndelag, Akershus and Oslo accounted for most of the cancer cases between 2015 to 2019 among men. However, for both males and females, the incidence and mortality have been declining since 1965, and the survival has moderately increased over time (5).

The cause of gastric cancer is estimated to result from a complex interaction between genetic predisposition, diet and infection (6). Up to 80% of non-cardia gastric cancer have been estimated to be caused by *Helicobacter Pylori* (*H. Pylori*) which cause an infection in the stomach (7). *H. Pylori* infection increases the risk of gastric cancer via the indirect and the direct effect (8). The indirect effect is through a chronic inflammatory process where persistent inflammation can lead to atrophic gastritis and peptic ulcer disease (PUD), which are well-known risk factors for developing gastric cancer (9, 10).

The direct effect is due to the toxic action of virulence factors from *H. Pylori*. These virulence factors can cause mutations of cell-cycle regulating genes and deficiencies in DNA repair mechanism. Studies in animals have also shown an increased mutation rate in gastric mucosa infected with *H. Pylori* (8).

As for genetic predisposition, hereditary diffuse gastric cancer accounts for about 1-3% of cases, while familial gastric cancer are observed in about 10% of all the gastric cancer cases (6). The dietary factors that are associated with gastric cancer are high-salt and salt-preserved food (3).

1.2 Drugs for acid related disorders

Gastric acid produced from the parietal cells in the stomach plays a key role in digesting proteins from food. The function of parietal cell is to secrete intrinsic factor and hydrochloric acid which creates the acidic environment. The role of acetylcholine, gastrin and histamine is to stimulate the parietal cells to secrete hydrochloric acid and intrinsic factor, while somatostatin inhibits the secretion from parietal cells.

If the gastric acid exposes into deeper tissues and cells in the stomach as a result from high levels of gastric acid, or weakening of the mucus layer in the stomach, it could lead to stomach ulcers or acid reflux symptoms. In contrast, if the levels of gastric acid are too low, it may impair the ability of digesting food. Therefore, the gastric acid levels and the protective mucus layer should be in balance to avoid stomach ulcers or reflux symptoms.

The acidic environment in the stomach is also important to inhibit the growth of microorganisms, and thus helpful to prevent infections. Yet, *H. Pylori* can overcome the acidic environment to cause an infection by producing urea which leads to local alkalization and thereby protecting the bacteria from gastric acid (11).

PPI and H2RA are drugs that inhibits the gastric acid secretion and have a similar indication of use. However, *H. Pylori* infection is an indication solely for PPI while the common indication for PPI and H2RA are PUD, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome and non-steroidal anti-inflammatory drugs (NSAIDs) associated ulcers (12, 13).

Regarding mechanism of these drugs, PPIs binds to proton pumps in the parietal cells and inhibits the proton pumps from releasing protons (H^+ ions) into the lumen. As a result, PPI inhibits the final step of gastric acid secretion from a parietal cell regardless of acetylcholine, gastrin and histamine (14).

Although the primary aim for H2RA is to inhibit the gastric acid as well, the mechanism of H2RA differs from PPIs. H2RA binds to Histamine-2 receptor on the parietal cell and prevents histamine from stimulating the parietal cells to secrete gastric acid (15). In contrast to PPI, H2RA inhibits an earlier step of gastric acid secretion. Nevertheless, acetylcholine and gastrin could still stimulate the parietal cell to secrete gastric acid and explains why PPI is a more potent drug than H2RA (figure 1).

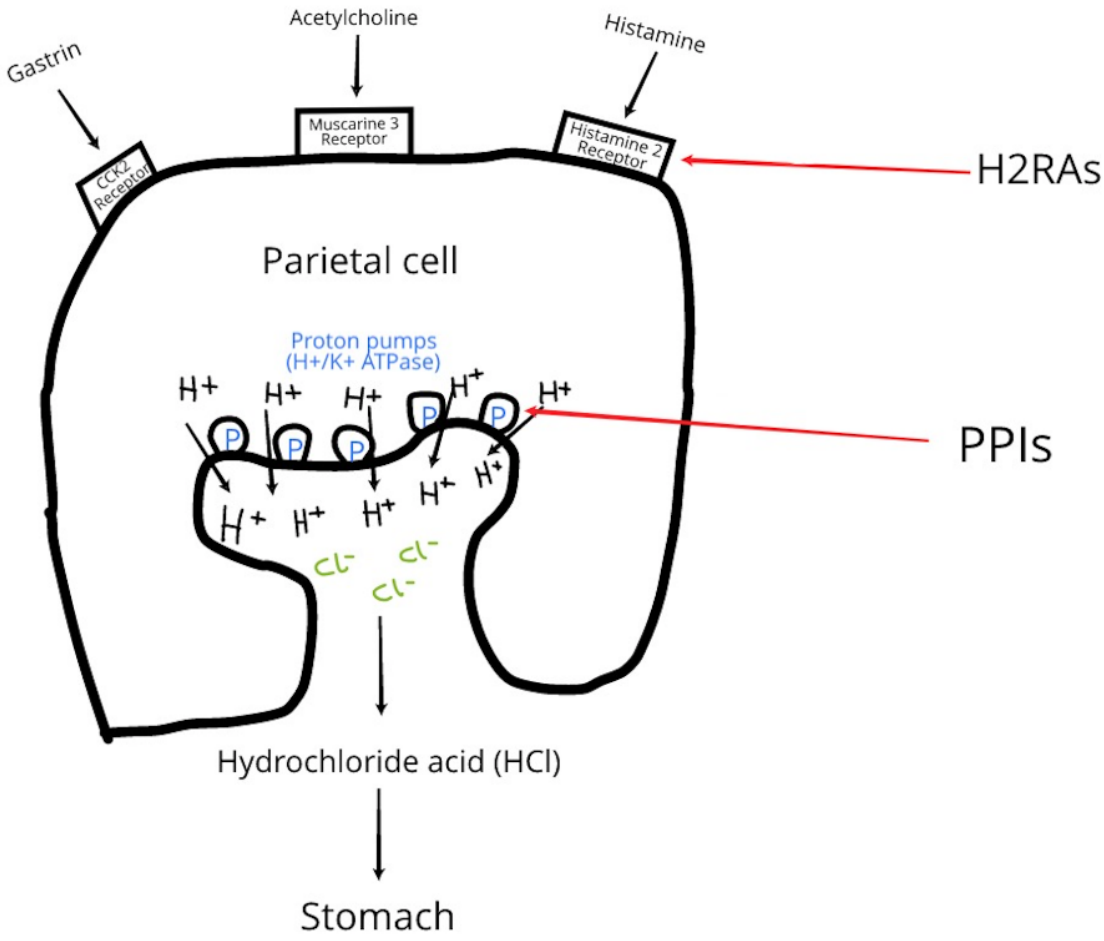

Figure 1 A simplified physiology of gastric acid secretion from parietal cells and the mechanism of action for PPIs and H2RAs. PPI, Proton Pump Inhibitor; H2RA, Histamine-2 Receptor Antagonist; H+, proton; Cl-, chloride ion; P, proton pump

1.3 The use of PPI and H2RA in Norway

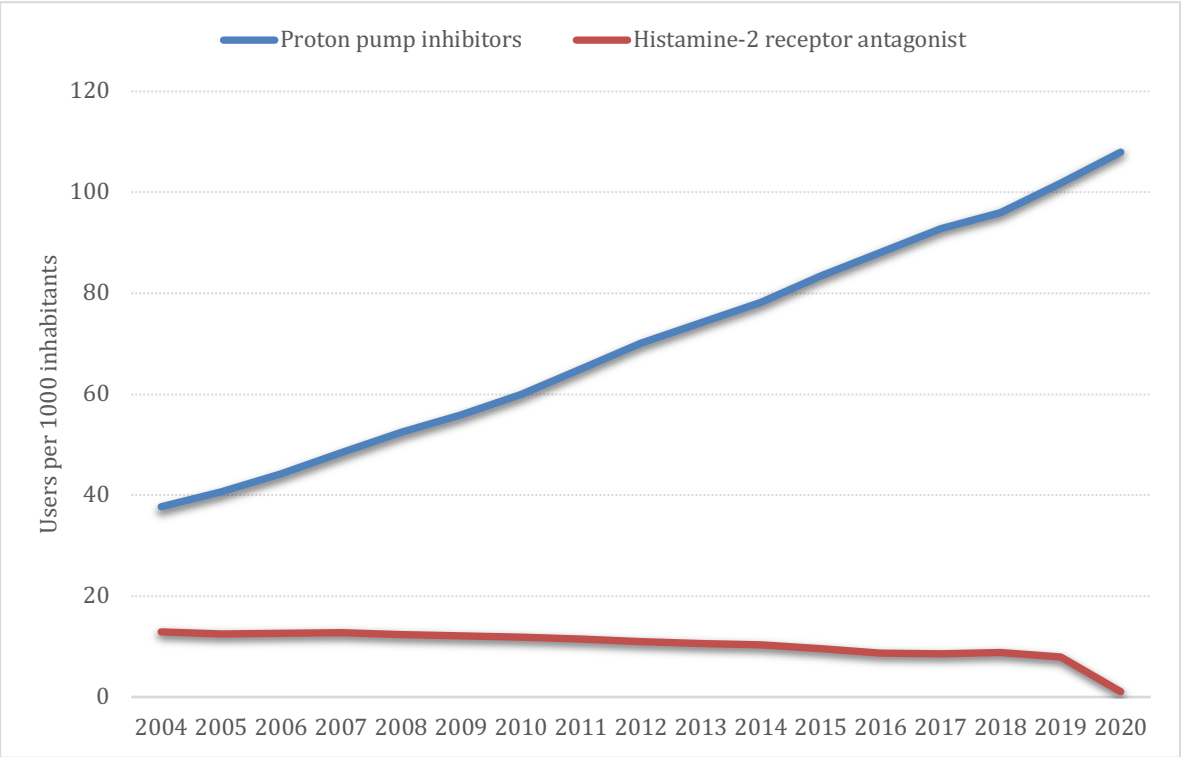

Figure 2 Proportion of PPI and H2RA users in Norway from 2004 to 2020. Over-the-counter drugs and the combination drug Vimovo (Naproxen and Esomeprazole) were not included (1).

The number of PPI users on prescription have more than doubled since 2004 while the number of H2RA users on prescription have been decreasing in Norway (figure 2). In 2020, 580 758 individuals received PPI on prescription at least once, which is approximately 10% of the Norwegian population. Within the same year, the proportion of PPI users increased with increasing age and most PPI users were females (figure 3). In addition, Northern Norway accounted for the majority of PPI users in Norway since 2004 (figure 4) (1).

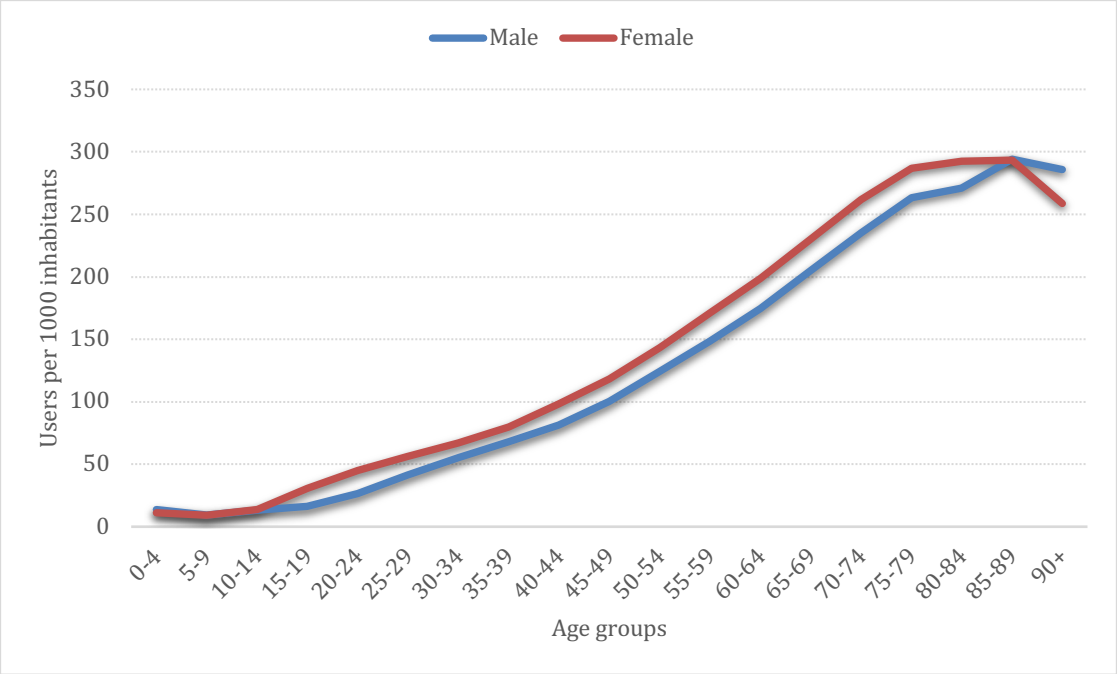

Figure 3 Proportion of PPI users in 2020 by age and sex. PPI over-the-counter and the combination drug Vimovo (Naproxen and Esomeprazole) were not included (1).

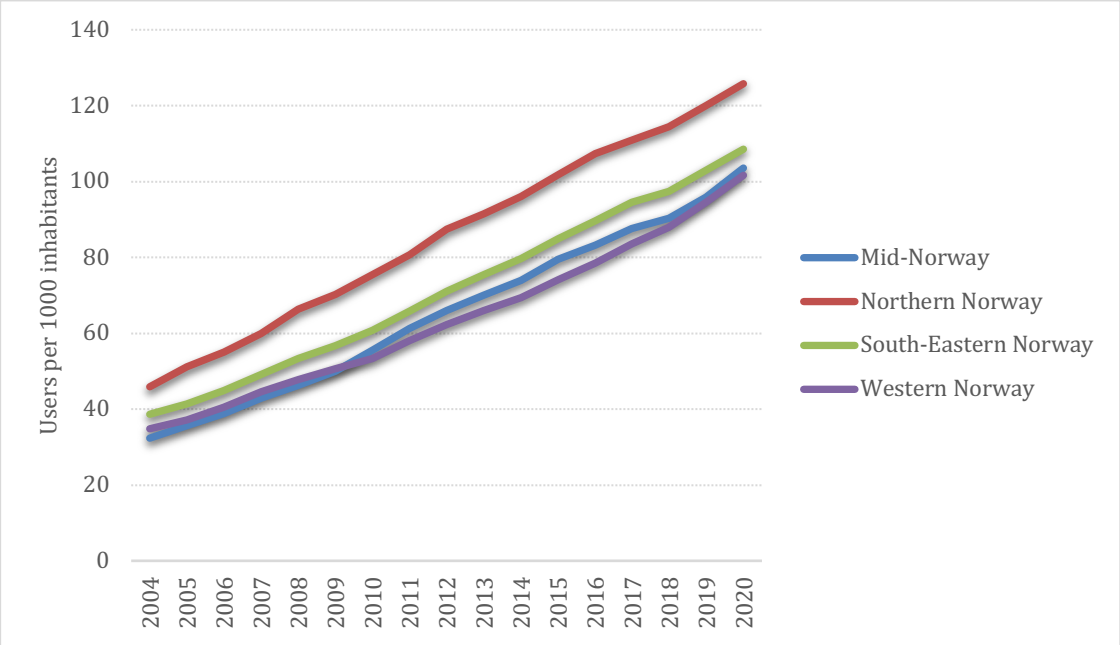

Figure 4 Proportion of PPI users in Norway from 2004 to 2020 by residency. PPI over-the-counter and the combination drug Vimovo (Naproxen and Esomeprazole) were not included (1).

1.4 PPI and H2RA use and gastric cancer

The association between PPI use and the increased risk of gastric has been observed in several studies, especially in observational studies and in vivo studies as well. However, clinical studies do not support this hypothesis, though there have not been many clinical studies investigating this hypothesis in contrast to observational studies.

As for observational studies, a meta-analysis from Qian-Yi Wan *et al (16)* concluded that long-term PPI use implied an approximately twofold risk for gastric cancer (OR=2.10, 95% Cl 1.10–3.09). Wan additionally categorized the risk into subgroups and found that participants with *H. Pylori* infection had an increased risk of gastric cancer (OR=5.01, 95% Cl -4.27-14.29).

Another study found that long-term PPI user was associated with an increased risk of gastric cancer in subjects even after *H. Pylori* eradication therapy (HR=2.44, 95% Cl 1.42-4.20). Moreover, the study was able observe a clear dose-response relationship. They found that daily use of PPIs was associated with a higher risk of gastric cancer (HR=4.55, 95% Cl 1.12-18.52) compared to weekly to < daily users (HR=2.43, 95% Cl 1.37-4.31) (17).

Potential bias and confounder such as immortal time bias, latency bias and Vitamin B_{12} deficiency among PPI users were mentioned that could affect the results of Cheung *et al* study (18, 19). However, one study included immortal time bias and latency bias and found that PPI use was still associated with an increased odds of gastric cancer (20), while the potential vitamin B_{12} confounder still remains unknown.

Previous studies that are probably relevant in a Norwegian context due to similar dietary habits and prevalence of *H. Pylori* is the Swedish study and Danish study. The Swedish study concluded that maintenance use of PPI was associated with an increased risk of gastric cancer (SIR=3.38, 95% Cl 3.25-3.53), while the Danish study observed an increased risk of gastric cancer among individuals who have received more than 15 prescriptions on PPI (IRR=2.1, 95% Cl 1.0-4.7). The Swedish study did also stratify the analysis into different indications and observed that the risk was especially increased in participants with *H. Pylori* infection (SIR=9.76, 95% Cl 8.87-10.71) and PUD (SIR=8.75, 95% Cl 8.12-9.41). Regarding H2RA, none of the two studies observed an increased risk of gastric cancer among H2RA users (21, 22).

A recent observational study included H2RA use in the analysis and observed an increased risk of gastric cancer among H2RA users (OR=1.44, 95% Cl 1.16-1.80). However, they suggested that the association between use of PPI and H2RA and the increased risk of gastric cancer was sensitive to the duration of lag-time used in the analysis. When the author applied 1-year lag time, the risk of gastric cancer was increased. But when the author used 2-year lag time, the association was attenuated, and thus concluded that they observed little consistent evidence on PPI use and the increased risk of gastric cancer (23).

Furthermore, some studies have investigated the duration-response relationship. All of these studies revealed a similar tendency, which is decreased risk estimates of gastric cancer when the duration of PPI use increases (16, 21, 23). From Wan's meta-analysis, the risk estimates of using PPI a year or less (OR=4.13, 95% Cl -1.80-10.07) was higher when compared to using PPI for 3 or more years (OR=1.01, 95% Cl 0.51-1.50). The authors from the Swedish study suggested that the decreased risk estimates indicated that long-term use of PPI probably protected against risk factors (*H. Pylori* and PUD) for developing gastric cancer.

In contrast to observational studies, clinical studies do not support the hypothesis between maintenance PPI use and gastric cancer development. In a meta-analysis which investigated six randomized controlled trials (RCT), the authors concluded that maintenance PPIs therapy was not associated with an increased gastric atrophic change or Enterochromaffin-like (ECL) cell hyperplasia. However, the authors stated that due to their protocol of the review, they excluded some potentially useful data from prospective non-randomized trials which had longer duration of follow-up that might be more valuable than RCTs in the assessment of premalignant lesions. However, this meta-analysis only assessed for long-term PPI use and the risk for premalignant lesions which is involved in the gastric cancer development.

As for the potential carsinogenic mechanism of PPIs and H2RA, there have been two in vivo studies in 1985 and 1986. Findings from these studies showed that Loxitidine (H2RA) and Omeprazole (PPI) induced gastric mucosa neoplasia among rodents, and thereby suggested that PPI and H2RA could play a role in the development of gastric cancer (24, 25).

Although in vivo studies were conducted in animals, hypergastrinemia and non-*H. Pylori* bacterial overgrowth has been addressed as potential carcinogenic mechanisms of PPIs among humans (26). Hypergastrinemia is a compensatory increase in gastrin production as a negative feedback due to the suppression of gastric acid production (27). The increased level of gastrin

drives the hyperplasia of ECL cells in the oxyntic mucosa which can lead to the formation of neuroendocrine tumors (NETs) (28).

Moreover, the lack of a gastric acid can lead to non-*H. Pylori* bacterial overgrowth in the stomach as a result of using PPIs. The overgrowth of non-*H. Pylori* bacteria in the stomach can lead to chronic inflammation and thus atrophic gastritis. It has been shown that non-*H. Pylori* bacterial overgrowth is a risk factor for atrophic gastritis (26, 29).

To summarize these findings, the results of many previous observational studies and in vivo studies have suggested that there is an association between long-term use of PPI and gastric cancer or that PPI and H2RA could play an important role in gastric cancer development. Possible carcinogenic mechanism supports this hypothesis as well. However, clinical studies do not support the relationship between long-term PPI and the risk of gastric cancer development.

In our study, the overall aim is to investigate if there is an association between PPI and H2RA use and risk of gastric cancer in a register-based study in an unselected population in Norway. We will thereby take the impact of several clinical and geographical factors into consideration.

2 Aims and hypothesis

The overall aim of this thesis is to evaluate whether there is an association between PPI and H2RA use and the risk of gastric cancer in a register-based study based on an unselected population. More specifically, we will investigate the following sub-aims:

1. Description of clinical and geographical factors as well as PPI and H2RA use in the study population
2. Evaluation of the association between the use of PPI and H2RA and the risk of gastric cancer adjusted for sex, age and date of diagnosis (by design) as well as *H. Pylori*, geography, education, comorbidity and other drug use
3. Evaluation of the risk for gastric cancer when using PPI compared to H2RA in an active comparator design

The public health perspective of identifying association between the use of PPI and H2RA and gastric cancer can reassure patients and prescriber about the safety of PPIs and H2RAs and promote their appropriate use, especially due to the increasing use of PPIs in Norway the last decade.

3 Material and Methods

3.1 Data sources

The Norwegian population is covered by a publicly funded healthcare system. Several national administrative and disease registries have been established that may be linked using a unique individual identification number assigned to all inhabitants of Norway. These Norwegian registries give a good prerequisite to conduct true population-based studies of diseases efficiently within this framework.

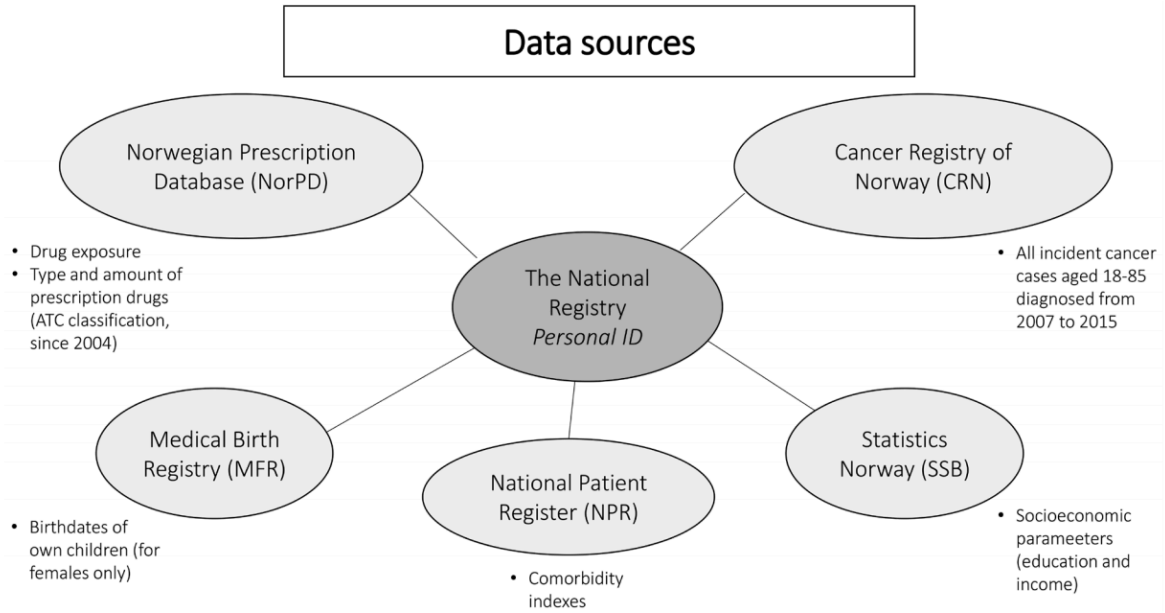

Figure 5 Data sources in the underlying study. ATC, Anatomical Therapeutic Chemical (30).

All adults residing in Norway aged 18-85 with a primary diagnosis of gastric cancer (C16) diagnosed between 2007 and 2015 were obtained from the Cancer Registry of Norway (CRN). The CRN has recorded incident cases of cancer nationwide since 1953. The registry has been shown to have accurate and almost complete ascertainment of cancer cases (31).

Information on the use of PPI and H2RA was provided by the Norwegian Prescription Database (NorPD). NorPD covers all prescription drugs dispensed to individuals in ambulatory care in Norway since 2004. The information also comprises the date, amount and county of the dispensed drug (32).

CRN and NorPD are the main data sources in this registry-based study. In addition, the Norwegian Patient Registry (NPR) provided data on comorbidity while Statistics Norway (SSB) gave information on education. In this case, we will use variables from all of these data sources to adjust for potentially confounding factors (figure 5).

The linkage process was organized like this: The CRN sent the Norwegian individual identification number and an internal identification number to all registries involved. All registries linked their information to the identification number and sent their information together with the internal identification number to the NorPD, which pseudonomized the data before sending it back to CRN.

3.2 Study design and study population

Experimental studies such as systematic reviews and meta-analyses are at the top of the evidence pyramid followed by experimental studies and observational studies such as cohort, case-control and nested case-control studies (33). Observational studies do not introduce an intervention or randomize the exposure and non-exposure group by chance in contrast to RCTs (experimental studies).

In this observational study, we used a nested case-control study design with risk-set sampling. A nested-case control study is a variation of case-control study where the cases and controls are drawn within an underlying cohort. The advantages of using a nested case-control study are that we can avoid or minimize selection, recall and information bias. The limitation of a nested case-control study is that the observed results only reveal an association only, and thus do not imply causal effects due to the possibilities of unknown or unobserved confounders.

The study population comprises all gastric cancer cases, diagnosed with gastric cancer (C16) in Norway between January 1st, 2007 and December 31st, 2015 and aged 18 to 85. Ten cancer-free controls were matched to each case with respect to birth year, sex and index date (date of diagnosis).

The control group is cancer-free individuals until index date but might get cancer later in life. By choosing ten controls per case, the uncertainty of the estimates are only negligibly larger than the uncertainty of the estimates in a cohort study (30).

3.3 Drug exposure

All drug exposure was based on prescriptions dispensed from 2004 and up to 1 year before the index date. Drug use was defined in two different ways: the crude exposure defining (long-term) users and non-users based on the total number of prescriptions and the cumulative exposure based on the cumulative DDDs.

We excluded PPI and H2RA use within 12 months before index date to avoid reverse causation as drug intake during this period could possibly be induced by early cancer symptoms. Reverse causation is when drug use is associated with cancer risk, but in the opposite direction of what we expect. For example, we expect that drug use will cause cancer, but as for reverse causation, cancer will cause the use of drug instead. In other words, PPI and

H2RA could be prescribed to treat early symptoms of a gastric cancer disease which is not yet diagnosed.

3.3.1 Users vs. Non-users

Drug users were defined as at least one prescription of PPI or H2RA between 2004 and up to one year before index date. Non-users are defined as not having used or received PPI or H2RA on prescription between 2004 and up to 1 year before index date.

3.3.2 Long-term vs. Non-users

Long-term drug use was defined based on the number of prescriptions filled from 2004 to one year before index date. Long-term use was defined as at least 8 prescription and short-term use as 1-7 prescriptions. Long-term use of PPI and H2RA corresponds to approximately two years of use assuming a duration of 3 months per prescription filled. Non-users are defined as not having used or received PPI or H2RA on prescription between 2004 and up to 1 year before index date.

3.3.3 Cumulative dose

The dose-response relationship was also evaluated for PPI and H2RA. Cumulative DDD, which is a variable that summarizes the total DDD for all prescriptions within the inclusion period, was grouped into a categorical variable.

All drug users were thus categorized into one out of 5 groups as shown in table 1. The reference group (1st quintile group) is the group of users with the lowest use and received at least one prescription of PPI or H2RA. The DDD limits for each group are presented in table 1 as well. The 2nd to the 5th quintile groups were compared to the reference group to assess the dose-response relationship.

Table 1 The DDD limits for each quintile groups. DDD; Defined daily dose; PPI, Proton Pump Inhibitor; H2RA, Histamine-2 Receptor Antagonist

Quintile	DDD limits for PPI	DDD limits for H2RA
1	4-27 (4 is the lowest dose)	3-15 (3 is the lowest dose)
2	28-11	16-30
3	12-427	31-90
4	428-1256	91-410
5	1257-9036	411-9920

We considered to analyze the cumulative DDD as a continuous variable, but this would have led to a mass distribution problem given mainly non-users. Excluding non-users from the analysis would lead to a dramatic decrease in power as all sets with a non-user case would be excluded. Moreover, not conditioning on matching anymore would introduce a bias because of an oversampling of cases. Thus, we decided to group the drug users in 5 user categories (non-users being the 6^{th} category) and used the lowest user category as a reference in the analysis when evaluating dose-response relationships.

3.3.4 ATC classification

Anatomical Therapeutic Chemicals (ATC) classification is a system that is used to classify the active ingredients of drugs according to which organ or system the active substance act, and their therapeutic, pharmacological and chemical properties. The active substances are thus classified in five different levels. The 1st level is classified into anatomical main group, 2nd level is the therapeutic subgroup, 3rd level the pharmacological subgroup and the 4th and 5th level is the chemical- subgroup and substance (34).

Given the ATC code A02B C02 as an example, the 2nd level comprises drugs for acid related disorders (ATC code: A02) while the 4th level is proton pump inhibitors (ATC code: A02 BC) (table 2).

Table 2 ATC codes for PPI and H2RA. ATC, Anatomical Therapeutic Chemical (35).

ATC levels	**ATC code**	**Active substance**
ATC 5th level for PPI	A02B C01	Omeprazol
	A02B C02	Pantoprazol
	A02B C03	Lansoprazol
	A02B C05	Esomeprazol
ATC 5th level for H2RA	A02B A01	Cimetidine
	A02B A02	Ranitidine
	A02B A03	Famotidine

3.4 Covariates

We will adjust for *H. Pylori* infection by identifying patients within the study who had undergone *H. Pylori* eradication therapy. From the Norwegian guidelines of treating *H. Pylori* infection, the therapy consists of treating with two of three antibiotics simultaneously (amoxicillin, metronidazole and clarithromycin; ATC codes: J01CA04, J01XD01 and J01FA09) plus a PPI (36). The method we used to identify *H. Pylori* patients was to include patients who received prescription on two of three antibiotics used in eradication therapy simultaneously or within the same month. The same method was used in the Danish study (22).

In addition, we adjusted for comorbidity measured by a modified version of Charlson Comorbidity Index (CCI) using the Patient Registry Index (PRI). The CCI is an approach to measure one-year mortality in patients who have may have a range of diseases based on the International Classification of Diseases. Each comorbidity is weighted differently (1 to 6), and CCI also takes the severity of a comorbidity into consideration. As an example, PUD is associated with lower weigh in contrast to malignant tumor which is associated with a higher weight. The scores are summed up to predict the one-year mortality for a patient. A higher score indicates to a higher risk of mortality or resource use while a lower score indicates to a decreased risk of mortality (37, 38).

The modified version of The CCI is an updated version of comorbidity index using the Norwegian PRI where the comorbidity index is weighted differently, and the conditions are either changed or adapted compared to conventional CCI. As an example, when age was considered in PRI, the comorbidity score was reduced for patients older than 50 years. PRI was also marginally better than the CCI to predict one-year mortality. Moreover, PRI are based on a more recent data in contrast to the CCI, and are thus more representative to the general population (39). All comorbidities (except cancer) of a patient up to two years before the index date were taken into consideration.

Education provided by SSB was also taken into consideration. We were able to adjust education into five different categories which are the primary/lower secondary, upper secondary, undergraduate, graduate/postgraduate and no education/missing. The education groups were compared to primary/lower secondary as a reference

Long-term use of other medications (other drug use), defined as whether the patients are long-term user of drugs from other drug groups than the ATC4-level of PPI and H2RA.

Residency was categorized according to the four health regions in Norway, which are North, Mid, West and South-East. The cases were categorized into residency by using information from the CRN, while the information for the controls was retrieved from the NorPD. The regions were compared to the South-East as a reference.

3.5 Statistical Methods

3.5.1 Stratified Cox regression

Given this nested case-control design, we applied a stratified Cox regression and received Hazard ratios (HRs), 95% confidence intervals (CIs) and corresponding *p*-values to evaluate the association between PPI/H2RA use and the risk of gastric cancer.

HR refers to the ratio between the hazard rate among the exposure group versus the hazard rates among the non-exposure group and can in our case be interpreted as the risk of gastric cancer in the drug group compared to non-user group. For example, HR above 1 indicates that PPI or H2RA use is associated with an increased risk of gastric cancer while a HR below 1 indicates a protective association.

We chose HRs instead of odds ratios because we have a timeline in addition to the binary outcome, since we require the controls to be event-free at the time of cancer diagnosis of the case (time-matched controls). Thus, we used a stratified Cox regression instead of a logistic regression model, which makes HR a better estimate compared to a traditional case-control study where the outcome is binary within a pre-defined time frame.

Interesting signals for PPI/H2RA use and gastric cancer will be defined based on p values, which combine information from the effect and sample size, variation in the data and will be compared to the type-I-error threshold $\alpha=0.05$. Associations with p-values below this threshold were considered to be significant associations.

3.5.2 Test for Association

To assess the PPI and H2RA use and gastric cancer risk, we will evaluate this association in four different analyses: binary drug use, long-term use, cumulative DDD and active comparator. Briefly, drug use and long-term use were compared to non-users while cumulative DDD was compared to the lowest use or at least one prescription of PPI/H2RA. Age, sex and index date are adjusted by design in all analysis. Finally, we will also adjust for *H. Pylori*, residency, education, comorbidity and other drug use.

Moreover, due to the same indication of use for PPI and H2RA, there will be individuals that have used both PPI and H2RA. For example, some individuals may have tried H2RA first without effect, and then changed to the more potent PPIs. Thus, we will adjust for H2RA use when assessing the association between PPI use and gastric cancer risk and vice versa.

H2RA was used as an active comparator to evaluate the association between PPI use and the risk of gastric cancer compared to H2RA use. As drug users might be different than non-users in many ways, confounding by indication can potentially bias the analyses. Thus, in the active comparator analysis we aim to compare PPI users with H2RA users when evaluating the association with risk of gastric cancer. PPI and H2RA use were thus compared between patient who had similar symptoms or diagnoses such as PUD or GERD. Figure 6 illustrates confounding by indication in our association analyses.

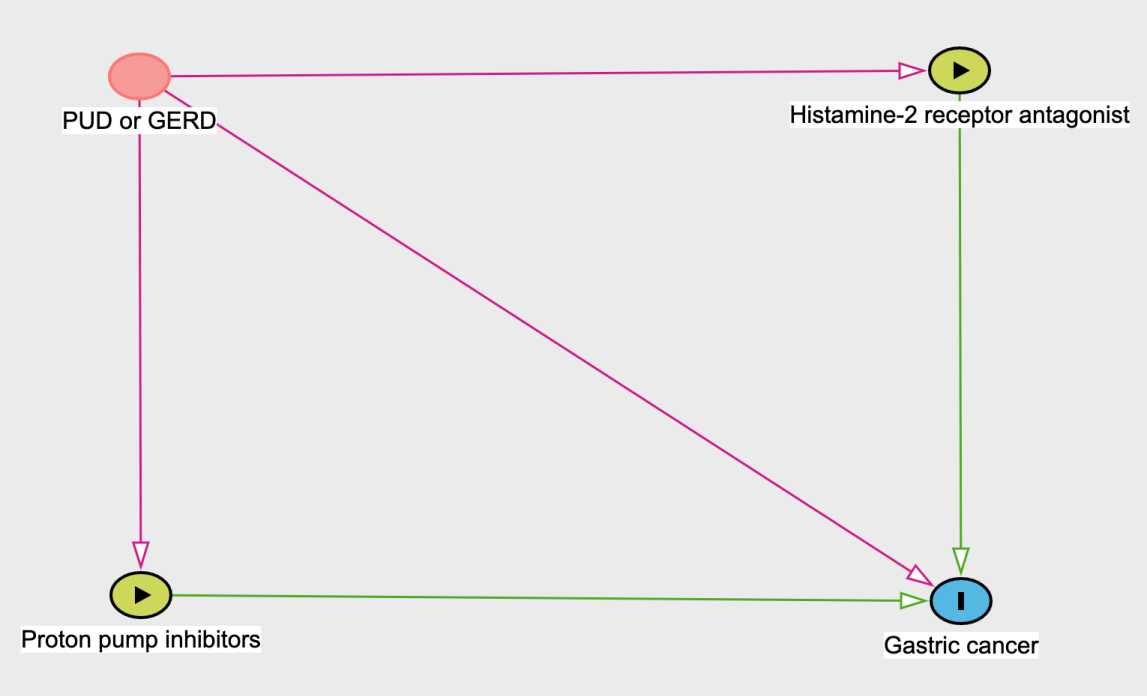

Figure 6 The effect of confounding by indication on the association between PPI and H2RA and gastric cancer. GERD, Gastroesophageal Reflux Disease; PUD, Peptic Ulcer Disease

3.5.3 Descriptive statistics

We presented results in tables and figures. Moreover, we presented percentage and median/Interquartile Range (IQR). IQR is the range between the lower and upper quartile when values are ordered from lowest to highest, and median is the value that separates the higher half from the lower half equally for a data set or a population. These quantities are robust against outliers.

4 Ethics

This study was approved by the Regional Ethical Committee (2016/352 Identifikasjon av karsinogene og kjemopreventive effekter av reseptpliktige legemidler) and the Norwegian data protection authority.

Furthermore, NorPD is a pseudonymized register which means that all birth numbers and health personnel number is replaced with a unique pseudonym for each individual in the study population so that they cannot be identified (40).

5 Results

5.1 Basic characteristics

In total there were 33 847 Norwegian individuals in this study, with 3 077 of them being cancer cases and 30 770 controls. Age (median 69; IQR 60-77) and sex (64% men) were equally distributed among gastric cancer and controls. In contrast, there was a higher percentage of cancer cases being *H. Pylori* positive (4%) and a higher percentage of cancer cases living in Western, Mid and Northern Norway (50%) when compared to controls (43%). There was also a higher percentage of comorbid patients among cancer cases (17%) and individuals using other drugs (70%) when compared to controls (table 3).

Table 3 Characteristics of gastric cancer cases and controls. H. Pylori, Helicobacter Pylori; Q1, Median of lower half; Q3, Median of upper half.

		Total (N=33 847)	**Cancer (N=3077)**	**Controls (N=30 770)**
Age	Median	-	69	69
	Q1, Q3	-	60, 77	60, 77
Sex	Female	12 210 (36%)	1110 (36%)	11 100 (36%)
	Male	21 637 (64%)	1967 (64%)	19 670 (64%)
H. Pylori	Negative	33 420 (99%)	2964 (96%)	30 456 (99%)
	Positive	427 (1%)	113 (4%)	314 (1%)
Region of residence	South-East Norway	18 356 (54%)	1501 (49%)	16 855 (55%)
	Western Norway	6557 (19%)	656 (21%)	5901 (19%)
	Mid Norway	4906 (14%)	495 (16%)	4411 (14%)
	Northern Norway	3464 (10%)	415 (13%)	3049 (10%)
	Unknown/missing region	564 (2%)	10 (0.3%)	554 (2%)
Education	Primary/lower secondary	10 260 (30%)	1105 (36%)	9155 (30%)
	Upper secondary	15 434 (46%)	1418 (46%)	14 016 (46%)
	Undergraduate	5334 (16%)	367 (12%)	4967 (16%)
	Graduate/postgraduate	2157 (6%)	125 (4%)	2032 (7%)
	No education/missing	662 (2%)	62 (2%)	600 (2%)
Comorbidity	0	29 031 (86%)	2537 (82%)	26 494 (86%)
	1-2	3180 (9%)	345 (11%)	2835 (9%)
	>2	1636 (5%)	195 (6%)	1441 (5%)
Other drug use	No	11 229 (33%)	938 (30%)	10 291 (33%)
	Yes	22 618 (67%)	2139 (70%)	20 479 (67%)

5.2 Drug use

Out of 33 847 study participants, there were 8 398 (25%) drug users in this study, more specifically 6 300 (19%) PPI users and 2 098 (6%) H2RA users. Among all PPI users, 1 084 (17%) individuals have also used H2RA while 5 216 (83%) are separate PPI users. As for H2RA users, more than half of H2RA users (1 014 individuals, 52%) have also used PPI.

There were more long-term users (8+ prescriptions) among cases than controls (11% vs. 8%). This trend is also visible in PPI and H2RA users separately (table 4).

Table 4 Characteristics of PPI and H2RA users. PPI, Proton Pump Inhibitor; H2RA, Histamine-2 Receptor Antagonist.

	Total (%)	**PPI (%)**	**H2RA (%)**
Numbers of drug use dispensed on prescription (N=33 847)			
Non-users	25 449 (75%)	27 547 (81%)	31 749 (94%)
1	2523 (7%)	1644 (5%)	879 (3%)
2-7	2961 (9%)	2210 (7%)	751 (2%)
8+	2914 (9%)	2446 (7%)	468 (1%)
Numbers of drug use dispensed on prescriptions among cancer (N=3077)			
Non-users	2071 (67%)	2324 (76%)	2824 (92%)
1	314 (10%)	211 (7%)	103 (3%)
2-7	358 (12%)	266 (9%)	92 (3%)
8+	334 (11%)	276 (9%)	58 (2%)
Numbers of drug use dispensed on prescriptions among controls (N=30 770)			
Non-users	23 378 (76%)	25 223 (82%)	28 925 (94%)
1	2209 (7%)	1433 (5%)	776 (3%)
2-7	2603 (8%)	1944 (6%)	659 (2%)
8+	2580 (8%)	2170 (7%)	410 (1%)

Figure 7 presents the number of PPI and H2RA prescriptions dispensed among gastric cancer and controls. Among the drug users, we identified 1 320 (16%) individuals with 8-14 prescription, 821 (10%) individuals with 15-24 prescriptions, 692 (8%) with 25-49 prescription and 81 (1%) who received more than 49 prescriptions on either PPI or H2RA.

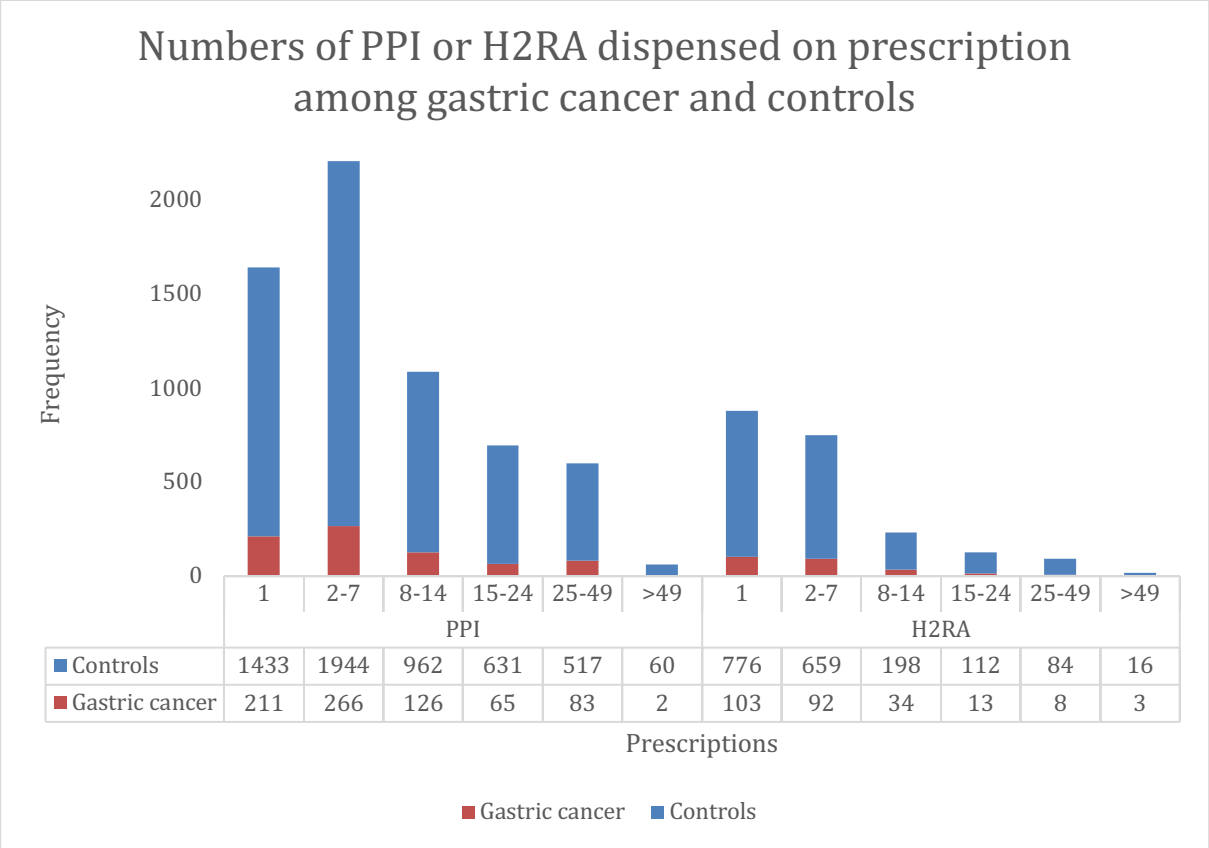

Figure 7 Number of PPI or H2RA dispensed on prescription among gastric cancer and controls. PPI, Proton Pump Inhibitor; H2RA, Histamine-2 Receptor Antagonist.

5.3 Other risk factors and PPI and H2RA use

The median age among H2RA users (median 72; IQR 63-79) was slightly higher when compared to PPI users (median 71; IQR 63-78), while there were a higher percentage of men (61%) among PPI users compared to H2RA users (57%). The existence of *H. Pylori* infection was verified in 5% (4%) of all PPI (H2RA) users. There was a higher percentage of H2RA users (54%) living in Western, Mid and Northern Norway when compared to PPI users (47%). We also identified a higher percentage of comorbidities among PPI users (28%) in comparison to H2RA users (25%). As a result, use of other drugs than PPI/H2RA was equally distributed between PPI and H2RA users (84%) (table 5).

Table 5 Characteristics of drug users and risk factors. PPI, Proton Pump Inhibitor; H2RA, Histamine-2 Receptor Antagonist; H. Pylori, Helicobacter Pylori; Q1, Median of lower half; Q3, Median of upper half.

		PPI (N=6300)	**H2RA (N=2098)**
Age	Median	71	72
	Q1, Q3	63, 78	63, 79
Sex	Female	2479 (39%)	908 (43%)
	Male	3821 (61%)	1190 (57%)
H. Pylori	Negative	5978 (95%)	2023 (96%)
	Positive	322 (5%)	75 (4%)
Region of residence	South-East	3361 (53%)	967 (46%)
	West	1236 (20%)	429 (20%)
	Mid	896 (14%)	356 (17%)
	North	807 (13%)	346 (17%)
	Missing	0 (0%)	0 (0%)
Education	Primary/lower secondary	2252 (36%)	800 (38%)
	Upper secondary	2939 (47%)	955 (46%)
	Undergraduate	810 (13%)	243 (12%)
	Graduate/postgraduate	222 (4%)	72 (3%)
	No education/missing	77 (1%)	28 (1%)
Comorbidity	0	4557 (72%)	1577 (75%)
	1-2	1068 (17%)	332 (16%)
	>2	675 (11%)	189 (9%)
Other drug use	No	1018 (16%)	330 (16%)
	Yes	5282 (84%)	1768 (84%)

5.4 Association of PPI use and risk of gastric cancer

In this study we found a significant impact of PPI use (HR=1.25, 95% Cl 1.13-1.37) and long-term use (HR=1.18, 95% Cl 1.03-1.36) on the risk of gastric cancer. However, we did not observe a dose-response relationship between PPI use and gastric cancer risk. When compared to the group with the lowest dose, there were no significant changes with respect to the risk of gastric cancer for higher dose groups (quintile 2-5). The trend effects for the 3rd to 5th quintile were stable (HRs=0.84-0.86) (table 6).

Table 6 Association between PPI use and the risk of gastric cancer. HR, Hazard ratio; Cl, Confidence interval; PPI, Proton Pump Inhibitor.

		HR*	95% Cl*	*P*-Value*
Drug use vs. non-use	Non-use	1.00	-	-
	PPI	1.25	1.13-1.37	$5.7 \cdot 10^{-6}$
Long-term use vs. non-use	Non-use	1.00	-	-
	1 prescription	1.37	1.17-1.60	$7.54 \cdot 10^{-5}$
	2-7 prescriptions	1.23	1.07-1.42	$4.55 \cdot 10^{-3}$
	8+ prescriptions	1.18	1.03-1.36	0.0199
Dose-response relationship	Quintile 1	1.00	-	-
	Quintile 2	1.08	0.85-1.36	0.533
	Quintile 3	0.84	0.66-1.07	0.155
	Quintile 4	0.86	0.67-1.09	0.210
	Quintile 5	0.86	0.68-1.10	0.234

*****The presented results are adjusted for H2RA use, *H. Pylori*, region of residence, education, comorbidity and other drug use

5.5 Association of H2RA use and risk of gastric cancer

Overall, we observed an increased risk trend for gastric cancer among H2RA users (HR=1.14; 95% Cl: 0.99-1.32). However, this result was not significant. Similarly, the results for long-term H2RA users and the dose-response relationship were not significant either. There was no visible trend in the effects (HRs) of higher dose drug use (quintile 2-5) when comparing to the group of lowers drug use (table 7).

Table 7 Association between H2RA use and the risk of gastric cancer. HR, Hazard ratio; Cl, Confidence interval; H2RA, Histamine-2 Receptor Antagonist.

		HR*	**95% Cl***	***P*-Value***
Drug use vs. non-use	Non-use	1.00	-	-
	H2RA	1.14	0.99-1.32	0.0704
Long-term use Vs. non-use	Non-use	1.00	-	-
	1 prescription	1.12	0.90-1.39	0.297
	2-7 prescriptions	1.15	0.91-1.44	0.241
	8+ prescriptions	1.18	0.89-1.57	0.252
Dose-response relationship	Quintile 1	1.00	-	-
	Quintile 2	0.91	0.60-1.38	0.655
	Quintile 3	0.87	0.58-1.32	0.513
	Quintile 4	1.12	0.76-1.67	0.569
	Quintile 5	0.73	0.47-1.12	0.152

*****The presented results are adjusted for PPI use, *H. Pylori*, region of residence, education, comorbidity and other drug use

In summary, PPI use and long-term use were significantly associated with an increased risk of gastric cancer. However, we did not observe a dose-response relationship. Despite the fact that there was a trend for H2RA use associated to an increased risk of gastric cancer, this was not supported by the analyses considering long-term use and dose-response relationship (figure 8).

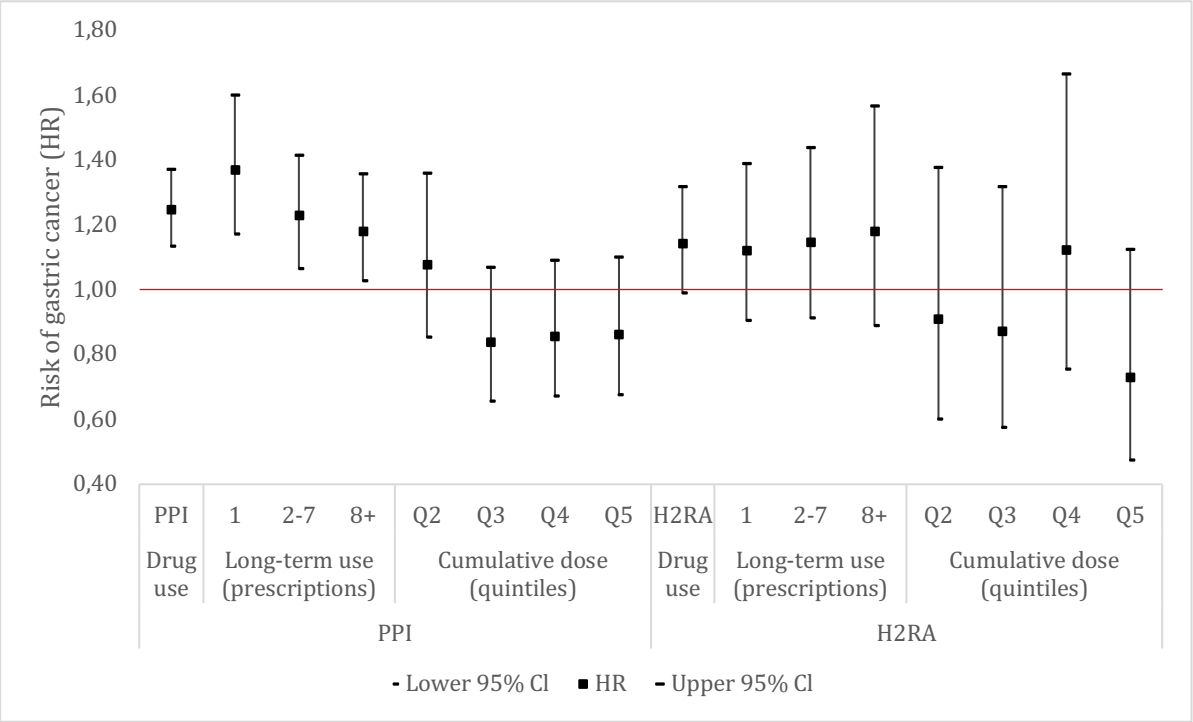

Figure 8 Association between PPI and H2RA and the risk of gastric cancer. HR, Hazard ratio; CI, Confidence interval; PPI, Proton Pump Inhibitor; H2RA, Histamine-2 Receptor Antagonist; Q2-Q5, Quintile 2-5.

5.6 Active comparator analysis

Table 8 presents the results of the active comparator analysis. We estimated the effect of separate PPI use versus separate H2RA use. The results revealed that the risk trend was not increased in PPI users compared to H2RA users (HR=0.98, 95% Cl 0.79-1.21).

Table 8 Association between H2RA in an active comparator and the risk of gastric cancer. HR, Hazard ratio; Cl, Confidence interval; PPI, Proton Pump Inhibitor; H2RA, Histamine-2 Receptor Antagonist.

		HR*	**95% Cl***	***p*-Value***
Active comparator	H2RA use (no PPI use)	1.00	-	-
	PPI use (no H2RA use)	0.98	0.79-1.21	0.839

*****The presented results are adjusted for *H. Pylori*, region of residence, education, comorbidity and other drug use

5.7 The role of other risk factors on the association between drug use and gastric cancer

The impact of other risk factors within the above association analyses was similar across all models applied (drug users, long-term users, dose-response and active comparator). Table 9 presents the results for the other risk factors in the analysis investigating the association between PPI use and the risk of gastric cancer. We found that individuals with positive *H. Pylori* had a significant impact on gastric cancer (HR=2.99, 95% Cl 2.38-3.75).

Residency in Northern Norway (HR=1.43, 95% Cl 1.27-1.61) also had a significant impact on gastric cancer followed by Mid (HR=1.24, 95% Cl 1.11-1.38) and Western Norway (HR=1.22, 95% Cl 1.11-1.35) when compared to South-East. Moreover, having a higher level of education (upper secondary or higher) was associated with a decreased risk of gastric cancer. In addition, we observed an increased risk of gastric cancer among comorbid PPI users (HR=1.08, 95% Cl 1.04-1.12) while we did not observe an impact of other drug use on the association between PPI and H2RA use and the risk of gastric cancer.

Table 9 Association between PPI use and the risk of gastric cancer adjusted for risk factors. HR, Hazard ratio; CI, Confidence interval; PPI, Proton pump Inhibitor; H. pylori, Helicobacter Pylori.

		HR*	95% CI*	p-Value*
Drug use vs. non-use	Non-use	1.00	-	-
	PPI	1.25	1.13-1.37	$5.7 \cdot 10^{-6}$
H. Pylori	Negative	1.00	-	-
	Positive	2.99	2.38-3.75	$2.22 \cdot 10^{-16}$
Region of residence	South-East Norway	1.00	-	-
	Western Norway	1.22	1.11-1.35	$5.13 \cdot 10^{-5}$
	Mid-Norway	1.24	1.11-1.38	$1.11 \cdot 10^{-4}$
	Northern Norway	1.43	1.27-1.61	$1.56 \cdot 10^{-9}$
	Unknown/missing region	0.19	0.10-0.37	$5 \cdot 10^{-7}$
Education	Primary/lower secondary	1.00	-	-
	Upper secondary	0.84	0.77-0.91	$3.91 \cdot 10^{-5}$
	Undergraduate	0.63	0.55-0.71	$3.83 \cdot 10^{-13}$
	Graduate/postgraduate	0.54	0.44-0.66	$5.12 \cdot 10^{-10}$
	No education/missing	1.14	0.86-1.51	0.348
Comorbidity	No	1.00	-	-
	Yes	1.08	1.04-1.12	$7.77 \cdot 10^{-5}$
Other drug use	No	1.00	-	-
	Yes	1.03	0.94-1.13	0.477

*****The presented results are adjusted for H2RA use

6 Discussion

We have presented the results for our population-based nested case-control study investigating the association between the use of PPI and H2RA and the risk of gastric cancer involving 33 847 residents in Norway. To our knowledge, the associations between the use of PPI and H2RA and gastric cancer risk have not been investigated in a population-based study in Norway before.

6.1 Discussion of results

We observed an association with increased risk of gastric cancer among PPI users and long-term PPI users in Norway. However, we did not observe any dose-response relationship between PPI use and gastric cancer risk. The corresponding results for H2RA use, long-term use and dose-response relationship were not significant. When comparing PPI use directly with H2RA use in an active comparator design, we did not observe a significant association between PPI use and the risk of gastric cancer.

Our significant results for long-term PPI use and gastric cancer risk were similar to previous observational studies. As an example, the Swedish study observed an increased risk of gastric cancer among individuals who underwent maintenance therapy of PPI defined as cumulative DDD of at least 180 days, while the authors in Cheung´s study found that the risk of gastric cancer was still increased after *H. Pylori* eradication therapy among long-term PPI users (17, 21). As for the PPI use and gastric cancer risk, our result is consistent with a recent observational study from the United Kingdom where they observed an increased risk of gastric cancer among PPI users (23).

The most plausible hypothesis for establishing a causal relationship between long-term PPI use and development of gastric cancer is hypergastrinemia (41). Hypergastrinemia is a compensatory increase in gastrin production as a response to the suppression of gastric acid. A recent study found a significant increase of serum gastrin after a four-day PPI-therapy among healthy volunteers (42). The increased level of gastrin is associated with the formation of NETs (28).

In addition, our results of dose-response relationship between PPI use and the risk of gastric cancer is consistent with the recent study from the United Kingdom where they also did not observe a dose-response relationship for PPI (23). In contrast, Cheung´s study observed a significant dose-response relationship between PPI use and gastric cancer risk. However, PPI users were almost 10 years older than non-users in his study. Increased age is an important risk factor for gastric cancer and might have influenced his results (43). Moreover, the study population in Cheung's study was mainly of Chinese origin. This could imply that Cheung´s finding may not be applicable to other ethnic groups as Asians are at higher risk of gastric cancer compared to the western population (44). However, the lack of a dose-response relationship for PPI in our study could also indicate that confounding by indication is influencing our significant result for (long-term) PPI use and gastric cancer risk.

Our corresponding results for H2RA use, long-term use and dose-response relationship were not associated with gastric cancer risk which was consistent with findings from the Danish and Swedish study (21, 22). A possible explanation is that PPI is a more potent drug and may give more side effects compared to H2RA. In addition, we only identified 2098 (6%) H2RA users in our study and this leads to a lower power for the analysis compared to the association analysis on PPI use and the risk of gastric cancer. Yet, the recent observational study from the United Kingdom found that H2RA use was significantly associated with an increased risk of gastric cancer (OR=1.44, 95% Cl 1.16-1.80). In contrast to the Danish and Swedish study, the recent study from the United Kingdom was not adjusted for *H. Pylori* (23).

The Danish and Cheung´s study were also consistent with our findings of the active comparator analysis as none of us did observe a significant difference in the risk of gastric cancer when comparing PPI users to H2RA users (17, 22). To observe a significant impact on the risk of gastric cancer when comparing PPI users to non-users, but not when comparing to H2RA users signifies that the indication has influenced the results of PPI users vs. non-users analysis. Thus, this could mean that our observed association between PPI (long-term) use and the risk of gastric cancer is influenced by confounding by indication. As an example, diseases such as *H. Pylori* and PUD are indications for PPI use and important risk factors in developing gastric cancer (45).

In our study we also observed a significant impact of a positive *H. Pylori* result on the risk of gastric cancer among PPI users. This was not surprising as *H. Pylori* is heavily associated with gastric cancer (46). This also indicates the importance of identifying individuals with *H. Pylori* when trying to disentangle the effect of *H. Pylori* on the association of drug use and the risk of gastric cancer. However, we only identified 427 (1%) individuals with positive *H. Pylori* in our study with a higher percentage of *H. Pylori* among cases (4%) compared to controls (1%). Although the exact prevalence of *H. Pylori* in Norway is unknown, it is estimated to be approximately 10-40% (47).

We therefore believe that we were not able to identify all positive *H. Pylori* individuals. The main reason is that we identified *H. Pylori* by individuals who had undergone eradication therapy instead of endoscopy with biopsy, which is the preferable method to diagnose *H. Pylori* (48). Second, when we first tried to identify individuals who received eradication therapy (2 antibiotics + PPI) on prescription, we only managed to identify approximately 100 individuals with positive *H. Pylori* between 2004 and 2015. We then chose to exclude PPI from our inclusion criteria and only included individuals who received two of three antibiotics used in eradication therapy. The same method was used in the Danish study (22). In this case, we identified more cases of *H. Pylori*, but most likely not all cases of *H. Pylori* in Norway. Finally, individuals who underwent eradication therapy in hospital were not included as NorPD only covers the ambulatory care.

Not being able to identify all individuals with treated or untreated *H. Pylori* infection at the time could potentially influence our findings, because *H. Pylori* is an important confounding factor on the association between PPI and gastric cancer.

Moreover, we observed that residency in Northern Norway in particular, but also in Mid and Western Norway was associated with an increased risk of gastric cancer among PPI users compared to South-East of Norway. We believe that residency partly reflects the prevalence of *H. Pylori* in different regions. Relevant lifestyle factors such as diet also differs across Norway. A Norwegian study have suggested that there are different food patterns in Norway and this pattern may reflect where in the country you live. As an example, the Norwegian coastline has easy access to fish and thus a higher fish consumption in contrast to the inner parts of Norway (49).

We also know that the majority of PPI users since 2004 are living in Northern Norway (1) although we only identified 807 (13%) PPI users from the North. The frequent use of PPI might also support a higher prevalence of *H. Pylori* in the North and might explain the increased risk of gastric cancer.

Another explanation of the residency factor is that the distance to the nearest health institution for individuals living in the North is usually longer compared to South-East, West and Mid of Norway. This could make the threshold for seeking medical attention higher in the North and might explain the increased risk of gastric cancer. However, we were unable to adjust for smoking, alcohol intake, obesity measured by body mass index and genetic factors which are risk factors for developing gastric cancer (45, 50, 51).

Regarding education, we observed that having a higher educational level (upper secondary or higher) was associated with a decreased risk of gastric cancer. Similar findings were found in Lagergren *et al* study where they suggested that higher educational level makes people more health-conscious (52).

Furthermore, it is not unusual to use PPI in combination or supplement with other drug groups such as antibiotics (eradication therapy for *H. pylori*) or NSAIDs to prevent ulcer (one of the indications for PPIs). Using other drugs in combination with PPI/H2RA could impact our results. As an example, NSAIDs have been shown to be associated with a decreased risk of gastric cancer (53). Despite that we identified that 84% of PPI and H2RA users used other drugs than PPI or H2RA, we did not observe a significant impact on gastric cancer for this group.

In summary, we found an association between PPI use and long-term PPI use and the increased risk of gastric cancer. However, we did not find a dose-response relationship, which therefore supports the rationale that well known risk factors such as *H. Pylori* were associated with both PPI use and increased risk of gastric cancer (confounding by indication). Furthermore, the active comparator design did not reveal any difference between PPI and H2RA use. This conclusion is also supported by the Danish study where they observed an increased risk of gastric cancer among individuals who have received more than 15 prescriptions on PPI, but the authors concluded that their findings were likely to result from confounding by indication (22).

Systematic reviews of RCTs did not suggest an association between long-term PPI use and the risk of gastric premalignant lesions. However, the numbers of included participants were small, and the follow-up time was relatively short (maximum 36 months) in the clinical studies (54).

6.2 Discussion of methods

We acknowledge that our observational study reveals statistical association only, and not implying a causal relationship between PPI use and the risk of gastric cancer due to unknown or unobserved confounders. However, observational studies are able to assess research questions in an unselected population in contrast to experimental studies such as RCTs and are thus an important supplement to RCTs.

Our study had the advantage of collecting information on the Norwegian population based on high quality registry data, which includes complete data on drug prescription and cancer diagnosis. This method will counteract for information and recall bias as individuals do not have to report their own drug use or cancer diagnosis. As a result, we included all Norwegian individuals with a primary diagnosis of gastric cancer from 2007 to 2015, and thus avoiding selection bias.

Furthermore, we took reverse causation into consideration and introduced a 12-month lag time while previous studies have operated with 6 to 24 month-lag time (17, 21-23). However, a recent study suggested that 6 months lag was sufficient (55).

A limitation of our study was that we did not have information on PPI and H2RA use before 2004. Not having information on drug use before 2004 potentially weakens the associations found in our study as some of the non-users could have been former PPI or H2RA users. We were also not able to include individuals who have used PPI or H2RA over-the-counter. Moreover, NorPD does not provide information on compliance. This means that there is no guarantee that individuals are actually using the drug after they received PPI or H2RA on prescription.

7 Conclusion

To conclude, our findings do not support a causal relationship between PPI use and the risk of gastric cancer in Norway. However, we cannot rule out this hypothesis. Observational studies adjusted for relevant confounders, in particular *H. Pylori* and PUD, or larger clinical studies with a longer follow-up are needed to evaluate this hypothesis in the future.

8 Reference

1. Norwegian Prescription Database. Statistics from the Norwegian Prescription Database: The Norwegian Institute of Public Health (NIPH); 2021 [cited 2021 05/06]. Available from: http://www.norpd.no/Prevalens.aspx
2. Organization WH. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) 2019 [cited 2021 12/11]. Available from: https://icd.who.int/browse10/2019/en#/C00.
3. World Cancer Research/American Institute for Cancer Research. Diet, nutrition, physical activity and stomach cancer 2018 [cited 2020 12/15]. Available from: https://www.dietandcancerreport.org
4. Organization WH. Cancer 2021 [updated 21/03/03; cited 2021 04/10]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer.
5. Cancer Registry of Norway. Cancer in Norway 2019 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway; 2020.
6. Norsk Elektronisk Legehåndbok (NEL). Ventrikkelkreft 2020 [updated 20/07/20; cited 2021 05/10]. Available from: https://legehandboka.no/handboken/kliniske-kapitler/magetarm/tilstander-og-sykdommer/magesekk/ventrikkelkreft/.
7. de Muckadell OS. Ulcus pepticum og cancer ventriculi-infektionssygdomme fremkaldt af Helicobacter pylori? Ugeskrift for læger. 2002;164:5945-6.
8. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: a state of the art review. Gastroenterology and hepatology from bed to bench. 2015;8(Suppl1):S6.
9. Hansson L-E, Nyrén O, Hsing AW, Bergström R, Josefsson S, Chow W-H, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. New England Journal of Medicine. 1996;335(4):242-9.
10. Correa P, Haenszel W, Cuello C. Tannenbaum. S., and Archer, M. A model for gastric cancer epidemiology. Lancet. 1975;2(7924):58-60.
11. Scott DR, Marcus EA, Weeks DL, Sachs G. Mechanisms of acid resistance due to the urease system of Helicobacter pylori. Gastroenterology. 2002;123(1):187-95.
12. Omudhome Ogbru. Proton Pump Inhibitors (PPIs): MedicineNet; April 2021 [updated 19/11/25; cited 2021 05/05]. Available from: https://www.medicinenet.com/proton-pump_inhibitors/article.htm
13. Electronic Medicines Compendium. Zantac Tablets 150mg. 2007 [updated 20/02/03; cited 2021 04/12]. Available from: https://www.medicines.org.uk/emc/product/219/smpc#INDICATIONS.
14. M Michel Wolfe. Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders: UpToDate 2021 [updated 20/06/13; cited 2021 04/12]. Available from: https://www.uptodate.com/contents/proton-pump-inhibitors-overview-of-use-and-adverse-effects-in-the-treatment-of-acid-related-disorders?search=pantoprazole&source=search_result&selectedTitle=3~80&usage_type=default&display_rank=1.
15. Vakil NB. Antiulcer medications: Mechanism of action, pharmacology, and side effects: UpToDate; April 2021 [updated 20/04/13; cited 2021 04/12]. Available from: https://www.uptodate.com/contents/antiulcer-medications-mechanism-of-action-pharmacology-and-side-effects?search=histamine%202%20receptor%20antagonists&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2939398644.
16. Wan Q-Y, Wu X-T, Li N, Du L, Zhou Y. Long-term proton pump inhibitors use and risk of gastric cancer: a meta-analysis of 926 386 participants. Gut. 2019;68(4):762-4.

17. Cheung KS, Chan EW, Wong AY, Chen L, Wong IC, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut. 2018;67(1):28-35.
18. Suissa S, Suissa A. Proton-pump inhibitors and increased gastric cancer risk: time-related biases. Gut. 2018;67(12):2228-9.
19. Gueta I, Halkin H, Markovits N, Loebstein R. Proton pump inhibitors and the risk for gastric cancer: possible confounding by serum vitamin B 12. Gut. 2018;67(10):1904-.
20. Lai S-W, Lai H-C, Lin C-L, Liao K-F. Proton pump inhibitors and risk of gastric cancer in a case–control study. Gut. 2019;68(4):765-7.
21. Brusselaers N, Wahlin K, Engstrand L, Lagergren J. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open. 2017;7(10):e017739-e.
22. Poulsen A, Christensen S, McLaughlin J, Thomsen RW, Sørensen HT, Olsen J, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. British journal of cancer. 2009;100(9):1503-7.
23. Liu P, McMenamin ÚC, Johnston BT, Murchie P, Iversen L, Lee AJ, et al. Use of proton pump inhibitors and histamine-2 receptor antagonists and risk of gastric cancer in two population-based studies. British Journal of Cancer. 2020:1-9.
24. Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion. 1986;35(Suppl. 1):42-55.
25. Poynter D, Pick C, Harcourt R, Selway S, Ainge G, Harman I, et al. Association of long lasting unsurmountable histamine H2 blockade and gastric carcinoid tumours in the rat. Gut. 1985;26(12):1284-95.
26. Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence. Therap Adv Gastroenterol. 2019;12:175628481983451.
27. Lundell L, Vieth M, Gibson F, Nagy P, Kahrilas P. Systematic review: the effects of long‐term proton pump inhibitor use on serum gastrin levels and gastric histology. Alimentary pharmacology & therapeutics. 2015;42(6):649-63.
28. Waldum HL, Sørdal Ø, Fossmark R. Proton pump inhibitors (PPIs) may cause gastric cancer–clinical consequences. Scandinavian journal of gastroenterology. 2018;53(6):639-42.
29. Sanduleanu S, Jonkers D, De Bruine A, Hameeteman W, Stockbrügger R. Double gastric infection with Helicobacter pylori and non‐Helicobacter pylori bacteria during acid‐suppressive therapy: increase of pro‐inflammatory cytokines and development of atrophic gastritis. Alimentary pharmacology & therapeutics. 2001;15(8):1163-75.
30. Andreassen BK, Støer NC, Martinsen JI, Ursin G, Weiderpass E, Thoresen GH, et al. Identification of potential carcinogenic and chemopreventive effects of prescription drugs: a protocol for a Norwegian registry-based study. BMJ open. 2019;9(4):e028504.
31. Larsen IK, Småstuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. European journal of cancer. 2009;45(7):1218-31.
32. Furu K. Establishment of the nationwide Norwegian Prescription Database (NorPD)--new opportunities for research in pharmacoepidemiology in Norway. Norsk epidemiologi. 2008;18(2).
33. Hoffmann T, Bennett S, Del Mar C. Evidence-based practice across the health professions-e-book: Elsevier Health Sciences; 2013.
34. WHO Collaborating Centre for Drug Statistics Methodology. ATC Structure and Principles [updated 2018/02/15; cited 2021 02/07]. Available from: https://www.whocc.no/atc/structure_and_principles/.

35. WHO collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2017 [updated 2020/12/17; cited 2021 02/07]. Available from: https://www.whocc.no/atc_ddd_index/?code=A02B&showdescription=no.
36. Helsedirektoratet. Ulcussykdom Oslo: Helsedirektoratet 2019 [updated 18/01/08; cited 2021 03/02]. Available from: https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus/abdomen/ulcussykdom.
37. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Clinical Epidemiology. 1987;40(5):373-83.
38. University of Manitoba. Concept: Charlson Comorbidity Index 2020 [updated 20/11/05; cited 2021 05/08]. Available from: http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?printer=Y&conceptID=1098.
39. Nilssen Y, Strand T-E, Wiik R, Bakken IJ, Yu XQ, O'Connell DL, et al. Utilizing national patient-register data to control for comorbidity in prognostic studies. Clinical epidemiology. 2014;6:395.
40. Helsedata. Reseptregisteret [cited 2021 01/26]. Available from: https://helsedata.no/no/forvaltere/folkehelseinstituttet/reseptbasert-legemiddelregister/.
41. Joo MK, Park J-J, Chun HJ. Proton pump inhibitor: The dual role in gastric cancer. World journal of gastroenterology. 2019;25(17):2058.
42. Helgadóttir H, Lund SH, Gizurarson S, Waldum H, Björnsson ES. Pharmacokinetics of single and repeated oral doses of esomeprazole and gastrin elevation in healthy males and females. Scandinavian Journal of Gastroenterology. 2021;56(2):128-36.
43. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiology and Prevention Biomarkers. 2014;23(5):700-13.
44. Organization WH. Cancer fact sheets: Stomach cancer: International Agency for Research on Cancer; 2020 [cited 2021 05/02]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf.
45. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Przeglad gastroenterologiczny. 2019;14(1):26.
46. Wroblewski LE, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clinical microbiology reviews. 2010;23(4):713-39.
47. Norsk Helseinformatikk (NHI). Helicobacter Pylori 2019 [updated 19/03/21; cited 2021 05/07]. Available from: https://nhi.no/sykdommer/magetarm/magesekk/helicobacter-pylori/.
48. Norsk Elektronisk Legehåndbok (NEL). Helicobacter Pylori (Hp) 2019 [updated 19/03/21; cited 2020 05/07]. Available from: https://legehandboka-no.mime.uit.no/handboken/kliniske-kapitler/infeksjoner/tilstander-og-sykdommer/bakteriesykdommer/helicobacter-pylori/#diagnosen.
49. Engeset D, Alsaker E, Ciampi A, Lund E. Dietary patterns and lifestyle factors in the Norwegian EPIC cohort: the Norwegian Women and Cancer (NOWAC) study. European journal of clinical nutrition. 2005;59(5):675-84.
50. He Z, Zhao T-T, Xu H-M, Wang Z-N, Xu Y-Y, Song Y-X, et al. Association between alcohol consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. Oncotarget. 2017;8(48):84459.
51. Yang P, Zhou Y, Chen B, Wan H-W, Jia G-Q, Bai H-L, et al. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. European journal of cancer. 2009;45(16):2867-73.

52. Lagergren J, Andersson G, Talbäck M, Drefahl S, Bihagen E, Härkönen J, et al. Marital status, education, and income in relation to the risk of esophageal and gastric cancer by histological type and site. Cancer. 2016;122(2):207-12.
53. Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC-Y. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. Journal of the National Cancer Institute. 2003;95(23):1784-91.
54. Eslami L, Nasseri-Moghaddam S. Meta-analyses: does long-term PPI use increase the risk of gastric premalignant lesions? Archives of Iranian medicine. 2013;16(8):0-.
55. Pottegård A, Hallas J. New use of prescription drugs prior to a cancer diagnosis. pharmacoepidemiology and drug safety. 2017;26(2):223-7.