Original research

Proton pump inhibitors and risk of gastric cancer: population-based cohort study

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► Additional online supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-325097).

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Received 5 May 2021
Accepted 18 June 2021
Published Online First 5 July 2021

To cite: Abrahami D, McDonald EG, Schnitzer ME, *et al*. *Gut* 2022;**71**:16–24.

ABSTRACT

Objective To determine whether new users of proton pump inhibitors (PPIs) are at an increased risk of gastric cancer compared with new users of histamine-2 receptor antagonists (H2RAs).

Design Using the UK Clinical Practice Research Datalink, we conducted a population-based cohort study using a new-user active comparator design. From 1 January 1990 to 30 April 2018, we identified 973 281 new users of PPIs and 193 306 new users of H2RAs. Cox proportional hazards models were fit to estimate HRs and 95% CIs of gastric cancer, and the number needed to harm was estimated using the Kaplan-Meier method. The models were weighted using standardised mortality ratio weights using calendar time-specific propensity scores. Secondary analyses assessed duration and dose–response associations.

Results After a median follow-up of 5.0 years, the use of PPIs was associated with a 45% increased risk of gastric cancer compared with the use of H2RAs (HR 1.45, 95% CI 1.06 to 1.98). The number needed to harm was 2121 and 1191 for five and 10 years after treatment initiation, respectively. The HRs increased with cumulative duration, cumulative omeprazole equivalents and time since treatment initiation. The results were consistent across several sensitivity analyses.

Conclusion The findings of this large population-based cohort study indicate that the use of PPIs is associated with an increased risk of gastric cancer compared with the use of H2RAs, although the absolute risk remains low.

Significance of this study

What is already known on this subject?
- Previous observational studies suggest that the use of proton pump inhibitors is associated with an increased risk of gastric cancer, a disease with poor survival.
- However, all previous studies were limited by important methodological shortcomings, which may lead to an exaggeration of the reported risk between the use of proton pump inhibitors and gastric cancer.

What are the new findings?
- The use of proton pump inhibitors is associated with a 45% increased risk of gastric cancer compared with the use of histamine-2 receptor antagonists.
- Gastric cancer risk increased with cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation

How might it impact on clinical practice in the foreseeable future?
- In light of the overuse of proton pump inhibitors, physicians should regularly reassess the necessity of ongoing treatment.

INTRODUCTION

Acid suppressant drugs, which include proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), are commonly prescribed to manage the symptoms of several gastric conditions.[1–3] In recent years, PPIs have become increasingly popular,[4] in part due to their superior acid suppression and their perceived safety profile.[5 6] However, although controversial, there is some evidence that the use of PPIs may be associated with several adverse gastrointestinal-related health outcomes, including *Clostridium difficile* infection, enteric colonisation with multidrug-resistant organisms and gastric cancer.[7–20]

A possible association between PPI use and gastric cancer is biologically plausible, as PPIs are known to cause hypergastrinaemia, which may induce hyperplasia.[21 22] To date, several observational studies have examined the association between PPI use and gastric cancer incidence, all of which have reported elevated relative risks ranging from 1.06 to 3.61, aside from one null study (HR 1.01, 95% CI 0.88 to 1.16).[9–20] However, these studies had significant methodological shortcomings, which may have exaggerated their findings. The majority of studies compared PPI users to the general population, which likely introduced confounding by indication, while other studies introduced conclusion-altering time-related biases, such as immortal-time bias and time-window bias.[23–25]

Given that PPIs are one of the most commonly prescribed drug classes worldwide, and uncertainties relating to their association with gastric cancer remain, we conducted a large population-based cohort study to determine whether patients newly treated with PPIs are at an increased risk of gastric cancer compared with patients newly treated with H2RAs.

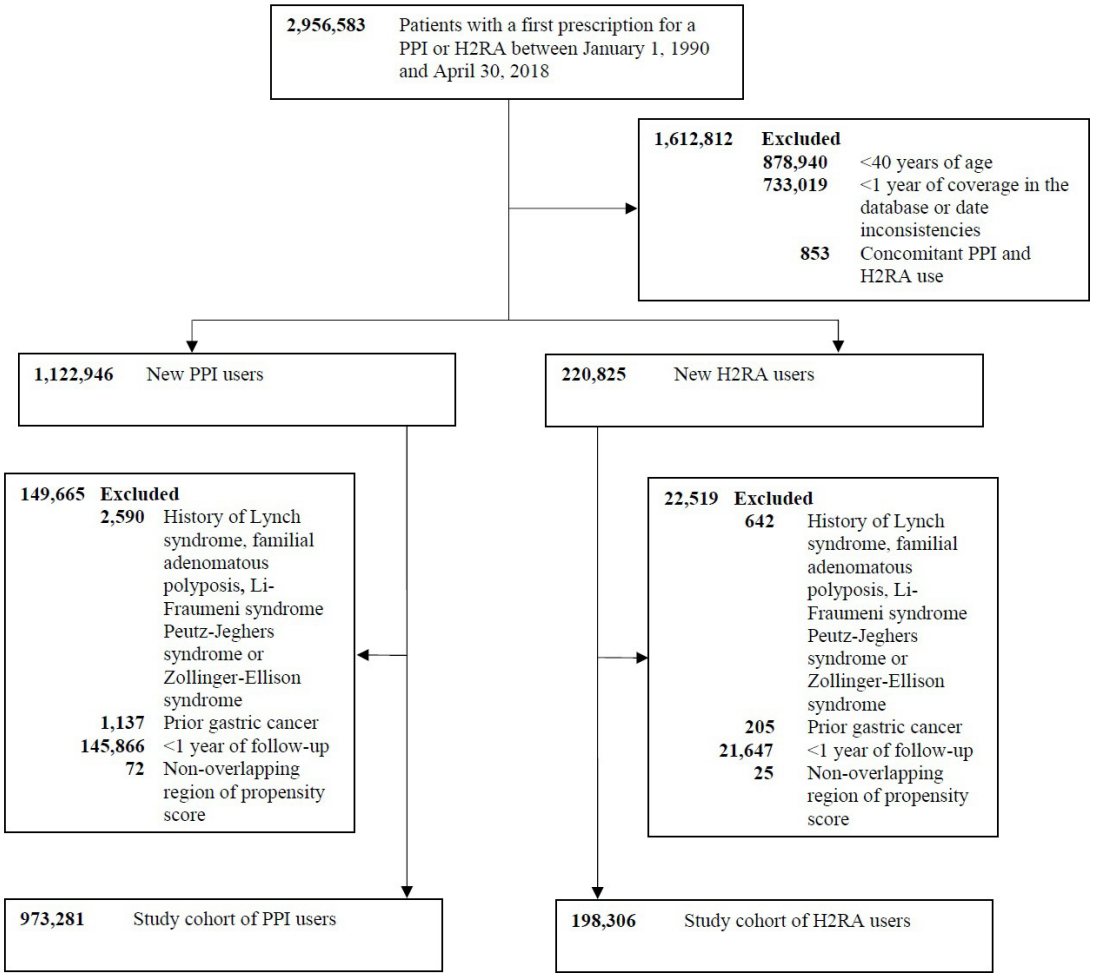

Figure 1 Study flow chart describing the construction of the proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) cohorts.

METHODS

Data source

This study was conducted using the UK Clinical Practice Research Datalink (CPRD). The CPRD is a large primary care database shown to be well representative of the general UK population, which contains the complete records of more than 15 million patients.[26 27] Recorded data includes patient characteristics, medical diagnoses, prescriptions and lifestyle characteristics. Cancer diagnoses have been previously validated, with positive predictive values for gastro-oesophageal cancers as high as 96%.[28–31]

Study population

We used a new-user, active comparator design where patients newly treated with PPIs were compared with patients newly treated with H2RAs. This active comparator was chosen to minimise confounding by indication, given that H2RAs are used for similar indications as PPIs. Cohort entry was defined as the date of the first prescription of either a PPI or an H2RA during the study period (identified using British National Formulary codes, online supplemental tables 1 and 2), from 1 January 1990 (first full year of PPI and H2RA availability) through 30 April 2018. At cohort entry, all patients were required to be at least 40 years old and have at least 1 year of medical information in the CPRD; the latter was necessary to identify new PPI and H2RA users. We excluded patients for whom a PPI and an H2RA were prescribed concomitantly at cohort entry, anyone with a history of gastric cancer (ie, to exclude prevalent cases), rare inherited cancer syndromes (Lynch syndrome, familial adenomatous polyposis, Li-Fraumeni syndrome or Peutz-Jeghers syndrome),[32] or Zollinger-Ellison syndrome (online supplemental figure 1). Finally, the cohort was restricted to patients with at least 1 year of follow-up after cohort entry (ie, 1-year lag period) to allow for a latency time-window and minimise detection bias and reverse causality.[33]

Exposure definition

All patients were followed starting 1 year after cohort entry until an incident diagnosis of gastric cancer (identified using Read codes (online supplemental table 3), 1 year after switching between the study drug classes (ie, switch from PPI to H2RA or vice versa to account for the 1-year lag period, with person-time during the lag period attributed to initial exposure), death from any cause, end of registration with the general practice, or end of the study period (30 April 2019), whichever occurred first. Patients were considered continuously exposed from cohort entry, regardless of treatment termination, as this exposure definition aligns with the hypothesised biological mechanism (ie, an irreversible effect of PPIs on gastric cancer development that persists even after treatment discontinuation).

Potential confounders

We considered a wide range of potential confounders, all measured on or before cohort entry. These included demographic

Table 1 Baseline characteristics of PPI and H2RA users before and after weighting

Characteristic	Before weighting			After weighting*		
	PPI	H2RA	ASD	PPI	H2RA	ASD
Total	973 281	198 306		973 281	972 083	
Age (mean, SD)	60.4 (13.0)	60.4 (13.1)	0.00	60.4 (13.0)	60.4 (28.9)	0.00
Male	438 592 (45.1)	85 505 (43.1)	0.04	438 592 (45.1)	436 521 (44.9)	0.00
Alcohol-related disorders	55 957 (5.8)	7912 (4.0)	0.08	55 957 (5.8)	56 352 (5.8)	0.00
Smoking status						
Current	260 166 (26.7)	50 856 (25.7)	0.03	260 166 (26.7)	259 094 (26.7)	0.00
Former	141 467 (14.5)	20 490 (10.3)	0.13	141 467 (14.5)	142 286 (14.6)	0.00
Never	538 106 (55.3)	100 006 (50.4)	0.10	538 106 (55.3)	537 236 (55.3)	0.00
Missing	33 542 (3.5)	26 954 (13.6)	0.37	33 542 (3.5)	33 467 (3.4)	0.00
Body mass index						
<25 kg/m^2	361 873 (37.2)	67 314 (33.9)	0.07	361 873 (37.2)	362 379 (37.3)	0.00
25–29.9 kg/m^2	326 240 (33.5)	58 226 (29.4)	0.09	326 240 (33.5)	325 379 (33.5)	0.00
≥30 kg/m^2	177 306 (18.2)	27 732 (14.0)	0.12	177 306 (18.2)	176 823 (18.2)	0.00
Missing	107 862 (11.1)	45 034 (22.7)	0.31	107 862 (11.1)	107 502 (11.1)	0.00
Atrial fibrillation	34 778 (3.6)	6037 (3.0)	0.03	34 778 (3.6)	35 576 (3.7)	0.00
Anaemia	89 930 (9.2)	14 860 (7.5)	0.06	89 930 (9.2)	90 836 (9.3)	0.00
Cancer	81 000 (8.3)	13 416 (6.8)	0.06	81 000 (8.3)	82 457 (8.5)	0.01
Congestive heart failure	21 292 (2.2)	6372 (3.2)	0.06	21 292 (2.2)	21 920 (2.3)	0.00
Gastric metaplasia	293 (0.0)	55 (0.0)	0.00	293 (0.0)	371 (0.0)	0.00
Hypercholesterolaemia	293 279 (30.1)	33 809 (17.1)	0.31	293 279 (30.1)	292 404 (30.1)	0.00
Hypertension	311 466 (32.0)	51 441 (25.9)	0.14	311 466 (32.0)	310 451 (31.9)	0.00
Venous thromboembolism	44 121 (4.5)	7944 (4.0)	0.03	44 121 (4.5)	44 645 (4.6)	0.00
Chronic kidney disease	54 247 (5.6)	4044 (2.0)	0.19	54 247 (5.6)	55 217 (5.7)	0.00
Stroke	49 495 (5.1)	10 105 (5.1)	0.00	49 495 (5.1)	50 673 (5.2)	0.01
Hernia	32 113 (3.3)	7586 (3.8)	0.03	32 113 (3.3)	33 737 (3.5)	0.01
Gastrointestinal bleeding	85 760 (8.8)	13 108 (6.6)	0.08	85 760 (8.8)	85 927 (8.8)	0.00
Dialysis	794 (0.1)	304 (0.2)	0.02	794 (0.1)	807 (0.1)	0.00
Gastric surgery	2678 (0.3)	645 (0.3)	0.01	2678 (0.3)	2854 (0.3)	0.00
Barrett's oesophagus	2928 (0.3)	79 (0.0)	0.06	2928 (0.3)	3627 (0.4)	0.01
Helicobacter pylori infection	20 440 (2.1)	982 (0.5)	0.14	20 440 (2.1)	20 935 (2.2)	0.00
Gastro-oesophageal reflux disease	86 985 (8.9)	17 461 (8.8)	0.00	86 985 (8.9)	90 581 (9.3)	0.01
Peptic ulcer disease	29 358 (3.0)	8623 (4.4)	0.07	29 358 (3.0)	29 795 (3.1)	0.00
Dyspepsia	169 147 (17.4)	60 869 (30.7)	0.32	169 147 (17.4)	173 000 (17.8)	0.01
Gastritis	41 343 (4.3)	11 094 (5.6)	0.06	41 343 (4.3)	42 142 (4.3)	0.00
Stomach pain	273 864 (28.1)	58 350 (29.4)	0.03	273 864 (28.1)	277 733 (28.6)	0.01
Metformin	56 972 (5.9)	6286 (3.2)	0.13	56 972 (5.9)	57 053 (5.9)	0.00
Non-steroidal anti-inflammatory drugs	692 208 (71.1)	123 534 (62.3)	0.19	692 208 (71.1)	689 062 (70.9)	0.01
Antiplatelets	231 359 (23.8)	37 483 (18.9)	0.12	231 359 (23.8)	232 216 (23.9)	0.00
Dual antiplatelets	67 206 (6.9)	9164 (4.6)	0.10	67 206 (6.9)	68 440 (7.0)	0.01
Cyclooxygenase-2 inhibitors	82 509 (8.5)	8622 (4.4)	0.17	82 509 (8.5)	82 734 (8.5)	0.00

Continued

Table 1 Continued

Characteristic	Before weighting			After weighting*		
	PPI	H2RA	ASD	PPI	H2RA	ASD
Prostaglandin analogues	1564 (0.2)	1101 (0.6)	0.07	1564 (0.2)	1692 (0.2)	0.00
Selective serotonin reuptake inhibitors	216 197 (22.2)	28 459 (14.4)	0.20	216 197 (22.2)	216 694 (22.3)	0.00
Anticoagulants	37 461 (3.9)	6718 (3.4)	0.02	37 461 (3.9)	38 322 (3.9)	0.00
Steroids	155 048 (15.9)	27 031 (13.6)	0.06	155 048 (15.9)	156 362 (16.1)	0.00
Year of cohort entry						
1990–1994	7839 (0.8)	33 809 (17.1)	0.59	7839 (0.8)	7857 (0.8)	0.00
1995–1999	36 611 (3.8)	50 456 (25.4)	0.65	36 611 (3.8)	36 711 (3.8)	0.00
2000–2004	148 408 (15.3)	62 201 (31.4)	0.39	148 408 (15.3)	148 453 (15.3)	0.00
2005–2009	327 938 (33.7)	30 027 (15.1)	0.44	327 938 (33.7)	328 102 (33.8)	0.00
2010–2018	452 485 (46.5)	21 813 (11.0)	0.85	452 485 (46.5)	450 960 (46.4)	0.00

Before weighting: counts (percentages), unless otherwise stated; after weighting: count, rounded to the nearest whole number, (percentages), unless otherwise stated.
*Pseudopopulation created by applying standardised mortality ratio weights from calendar time-specific propensity scores.
ASD, absolute standardised difference; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor;.

and lifestyle variables, such as age (modelled as a continuous variable using a cubic spline model to account for a possible non-linear relation with the outcome),[34] sex, alcohol-related disorders (alcohol dependency, alcoholic cirrhosis of the liver, alcoholic hepatitis, hepatic failure), smoking status, and body mass index. The potential confounders also included comorbidities, such as atrial fibrillation, anaemia, cancer (excluding non-melanoma skin cancer), congestive heart failure, gastric metaplasia, hypercholesterolaemia, hypertension, venous thromboembolism, chronic kidney disease, stroke, hernia, gastrointestinal bleeding, dialysis and gastric surgery. We considered approved indications for acid suppressant drug use (Barrett's oesophagus, *Helicobacter pylori* infection (identified by either a diagnosis or a prescription for triple therapy), gastro-oesophageal reflux disease, peptic ulcer disease, dyspepsia) and off-label indications (gastritis or duodenitis and stomach pain). We considered each indication separately, as there are some variations in the guidelines by indication.[35] Finally, we included the use of the following drugs: metformin, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, which have been associated with a decreased risk of gastric cancer,[36–38] antiplatelets, dual antiplatelets, selective serotonin reuptake inhibitors (SSRIs), anticoagulants and steroids, which may cause bleeding, and synthetic prostaglandin analogues, which are older drugs used to manage gastric conditions.[6] The aforementioned variables were selected based on a thorough review of the literature, which identified variables meeting the traditional definition of a confounder, measures of general health status and opportunities for interaction with healthcare providers (which may increase detection).[39]

Statistical analysis

The models were weighted using standardised mortality ratio weights estimated using calendar time-specific propensity scores.[40 41] The propensity scores were estimated using logistic regression as the predicted probability of receiving a PPI versus an H2RA conditional on the covariates listed above and within 5-year calendar year bands of cohort entry (1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2018). Calendar year bands were used to account for temporal changes in acid suppressant drug prescribing,[4] changes in gastric cancer incidence,[42] heterogeneity in covariate definitions during the study period. Calendar-time specific propensity scores may result in better confounding control compared with a single propensity score model.[41] Patients in non-overlapping regions of the propensity score distributions were trimmed.

Using the propensity scores, patients exposed to PPIs were given a weight of 1, while patients exposed to H2RAs were given a weight of the odds of the treatment probability (propensity score / (1-propensity score)).[40] This upweights the comparator patients (ie, H2RA users) to represent the treated population (ie, PPI users). Covariate balance was assessed before and after weighting using standardised differences, with differences of less than 0.10 indicative of good balance.[43]

We calculated crude incidence rates of gastric cancer with 95% CIs, based on the Poisson distribution, and constructed weighted Kaplan-Meier curves to compare the cumulative incidence of gastric cancer for PPI and H2RA users. The pseudocopulation created by weighting should balance the study covariates outlined above so that cumulative incidence of gastric cancer can be compared between PPI and H2RA users. Cox proportional hazards models were fit to estimate weighted HRs of gastric cancer with 95% CIs using robust variance estimators. We also

calculated the number needed to harm at five and 10 years of follow-up using the Kaplan-Meier method.[44]

Secondary analyses

We performed four prespecified secondary analyses. The first set of analyses modelled PPI use as a time-varying variable, updated at each person-day of follow-up, to determine whether the association varies by cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation. The cumulative duration was defined by summing the durations of each PPI prescription from cohort entry until the time of the risk set. To account for the different potencies of PPI types, we converted all PPI prescriptions to omeprazole equivalents using the WHO defined daily dose (online supplemental table 4).[45] Cumulative omeprazole equivalents were then calculated by summing the dose of each prescription from cohort entry until the time of each event-defining risk set. Finally, time since treatment initiation was defined as the time between the cohort entry until the time of the risk set. HRs for these secondary exposures were estimated according to predefined categories, and cumulative duration and dose were also modelled flexibly using restricted cubic spline models.[34] Second, we assessed the possibility of a drug-specific effect by stratifying the analyses by individual PPI molecules (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole or combinations). Third, we investigated possible effect measure modification by age and sex by including an interaction term in the model between exposure status and these variables. Finally, we calculated stratified HRs according to approved indications at baseline and within strata of the year of cohort entry.

Sensitivity analyses

We conducted six sensitivity analyses to assess the robustness of our findings. First, given uncertainties related to the optimal length of the latency time window, we repeated the primary analysis by increasing the exposure lag period to three, five and 10 years. Second, to assess the impact of informative censoring, we did not censor patients who switched from PPIs to H2RAs and vice versa (ie, analogous to an intention-to-treat exposure definition whereby patients are considered continuously exposed to their cohort entry drug until the end of follow-up). Third, as an alternative method to investigate the impact of informative censoring, we combined the standardised mortality ratio weights with stabilised inverse probability of censoring weights to account for censoring from drug switching during follow-up[46 47] and to account for the competing risk of death (online supplemental method 1).[48] Fourth, as certain H2RAs (such as ranitidine), have recently been found to be contaminated with N-nitrosodimethylamine (NDMA), a probable carcinogen,[49] we repeated the analysis with follow-up truncated on 31 December 2017, which is before the time NDMA contaminants were found.[49] Fifth, to investigate the impact of residual confounding, we repeated the primary analysis using the high-dimensional propensity score (HD-PS) approach to reweigh our study population (online supplemental method 2).[50] We considered all predefined covariates listed above, along with 200 empirically selected covariates from the HD-PS algorithm for this analysis. Finally, we conducted a post hoc sensitivity analysis to address the potential impact of residual confounding using the approach proposed by Ding and VanderWeele (online supplemental method 3).[51] All analyses were conducted with SAS V.9.4 (SAS Institute) and R (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

We did not include patients as study participants as our study involved the use of secondary data. Patients were not involved in the design or implementation of the study. We do not plan to involve patients in the dissemination of results, nor will we disseminate results directly to patients.

RESULTS

The cohort included 973 281 new PPI users and 198 306 new H2RAs users (figure 1). These exposure groups were followed for a median (Q1, Q3) duration of 5.1 (2.7, 8.4) and 4.2 (1.9, 8.3) years, respectively, including the 1-year lag period. There were 1166 incident gastric cancer events in the PPI cohort, which generated a crude incidence rate of 23.9 (95% CI 22.5 to 25.3) per 100 000 person-years. In the H2RA cohort, there were 244 incident gastric cancer events, which generated a crude incidence rate of 25.8 (95% CI 22.6 to 29.2) per 100 000 person-years.

Table 1 shows the baseline characteristics of the PPI and H2RA exposure groups. Before weighting, PPI users were more likely to be obese, have a prior diagnosis of hypercholesteraemia, chronic kidney disease, and *H. pylori* infection, but were less likely to have dyspepsia compared with H2RA users. PPI users were also more likely to have been prescribed NSAIDs, COX-2 inhibitors and SSRIs. Overall, most H2RA users entered the cohort earlier in the study period, while most PPI users entered later in the study period. After weighting, PPI users and H2RA users were well balanced on all study covariates (standardised differences below 0.10). During the follow-up period, H2RA users were more likely to have been censored due to a switch to a PPI than PPI users to a switch to H2RAs (56.2% vs 7.9%, respectively).

Table 2 shows the results of the primary and secondary analyses. While the crude HR was below the null value (HR: 0.92), the use of PPIs was associated with an increased risk of gastric cancer after adjusting for calendar year strata (HR: 1.34, 95% CI 1.14 to 1.57). In the fully adjusted model, the use of PPIs was associated with a 45% increased risk of gastric cancer, compared with the use of H2RAs (HR: 1.45, 95% CI 1.06 to 1.98). Similarly, PPI users had a higher cumulative incidence of gastric cancer than H2RA users. The weighted cumulative incidence curves diverged after two years of follow-up (or years after treatment initiation) (figure 2). The number needed to harm was 2121 and 1191 after five and 10 years after treatment initiation, respectively.

In secondary analyses, the HRs increased with cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation (table 2). These patterns were consistent in the restricted cubic spline models (online supplemental figures 2 and 3). The median (Q1, Q3) cumulative duration of PPI use was 139 days but was variable by indication, ranging from 130 (36, 715) days for *H. pylori* infection to 3.0 (1.3, 6.0) years for Barrett's oesophagus. The median (Q1, Q3) cumulative duration for H2RA users was 55 (30, 159) days, with minimal variation between the median value across the indications (range 30–92 days).

All PPI molecules were associated with elevated HRs for gastric cancer (ranging from 1.19 to 1.48; online supplemental table 5). While the point estimates increased with age (online supplemental table 6), and females had a slightly higher HR than males (online supplemental table 7) the CIs for these analyses were overlapping, which suggests no effect measure modification by age or sex. HRs were elevated among patients with gastro-oesophageal disease (HR 1.38, 95% CI 0.59 to 3.22) and peptic ulcer disease (HR 1.53, 95% CI 0.49 to 4.92) (online supplemental table 8). When stratifying by calendar year strata, there was some heterogeneity in the HRs (ranging from 0.87 to 2.55), though the CIs

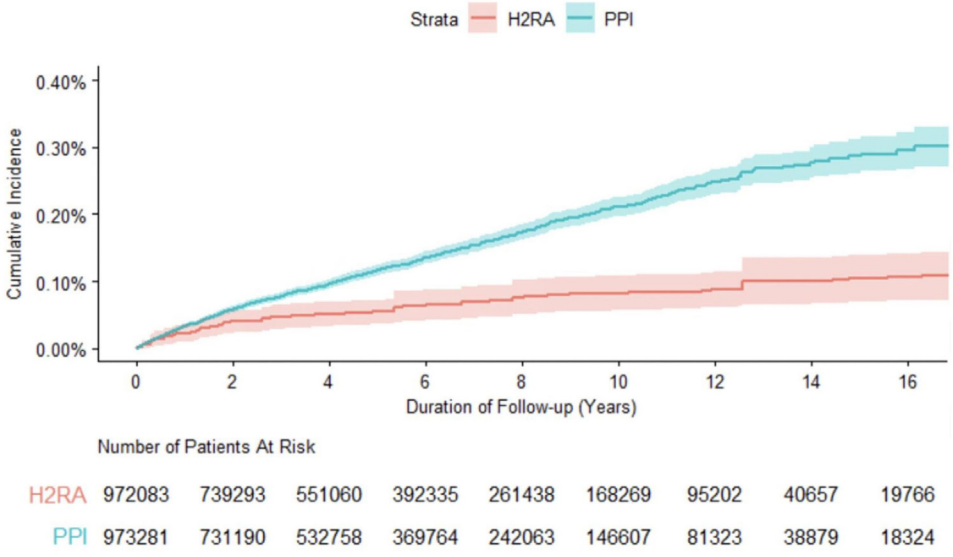

Figure 2 Weighted Kaplan-Meier curve illustrating the cumulative incidence of gastric cancer in patients newly prescribed proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RA). Follow-up starts 1 year after cohort entry. Curves are weighted using standardised mortality ratio weights: PPI patients are given a weight of 1, while H2RA patients are upweighted by the odds of the treatment probability.

for all strata were largely overlapping (online supplemental table 9).

Figure 3 summarises the results of the primary and sensitivity analyses (shown in detail in online supplemental tables 10–14). Overall, the findings were highly consistent with those of the primary analysis, with HRs ranging between 1.26 for the intention-to-treat analysis and 2.21 for the 10-year lagged analysis. Based on a post hoc analysis, an unmeasured confounder would need to be strongly related to both the exposure and outcome to nullify the observed association (online supplemental table 15).

DISCUSSION

Principal findings

In this large population-based cohort study, we observed that new users of PPIs are at a 45% increased risk of gastric cancer (HR 1.45, 95% CI 1.06 to 1.98) compared with new users of H2RAs, with a number needed to harm of 2121 and 1191 for five and 10 years after treatment initiation, respectively (figure 4). In secondary analyses, the risk increased with cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation. The results remained highly consistent across several sensitivity analyses that addressed different sources of bias.

Comparison with previous studies

The findings of this study are in line with those of several previous observational studies, with previous estimates ranging from 1.01 to 3.61,[9–20] including one study conducted using the same database.[16] However, our study used an active comparator and was explicitly designed to assess the comparative safety of PPIs versus H2RAs. This is a clinically relevant question that was not addressed by previous studies. Indeed, other studies may have overestimated the risk of PPIs on gastric cancer incidence by comparing PPI users to the general population,[9–19] given that patients with gastric conditions are already at an increased risk of

Table 2 Crude and adjusted HRs for the association between the use of PPIs and gastric cancer compared with the use of H2RAs

	Events	Person-years	Incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR (95% CI)	Marginal HR (95% CI) †
H2RAs (n=198 306)	244	947 418	25.8 (22.6 to 29.2)	1.00	1.00 (reference)	1.00 (reference)
PPIs (n=973 281)	1166	4 887 771	23.9 (22.5 to 25.3)	0.92	1.34 (1.14 to 1.57)	1.45 (1.06 to 1.98)
Cumulative duration of proton pump inhibitors						
<2 years	861	3 830 738	22.5 (21.0 to 24.0)	0.82	1.21 (1.03 to 1.42)	1.33 (0.96 to 1.83)
2–3.9 years	140	518 719	27.0 (22.7 to 31.8)	1.16	1.65 (1.31 to 2.07)	1.88 (1.33 to 2.65)
≥4 years	165	538 314	30.7 (26.2 to 35.7)	1.47	2.09 (1.67 to 2.62)	2.40 (1.68 to 3.45)
Cumulative omeprazole dose equivalents						
<14 600 mg	886	3 933 697	22.5 (21.1 to 24.1)	0.83	1.22 (1.04 to 1.43)	1.33 (0.97 to 1.83)
14 600–28 199 mg	147	502 892	29.2 (24.7 to 34.4)	1.27	1.81 (1.45 to 2.26)	2.05 (1.46 to 2.89)
≥29 200 mg	143	451 182	29.5 (24.7 to 34.9)	1.39	2.03 (1.60 to 2.58)	2.34 (1.62 to 3.37)
Time since proton pump inhibitor initiation						
<2 years	293	892 171	32.8 (29.2 to 36.8)	0.94	1.63 (1.17 to 2.29)	1.25 (0.69 to 2.28)
2–3.9 years	334	1 404 884	23.8 (21.3 to 26.5)	0.81	1.24 (0.92 to 1.67)	1.32 (0.79 to 2.19)
≥4 years	539	2 590 716	20.8 (19.1 to 22.6)	0.98	1.26 (1.01 to 1.56)	1.82 (1.09 to 3.02)

*Crude incidence rate per 100 000 person-years.
†Weighted using standardised mortality ratio weights.
H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

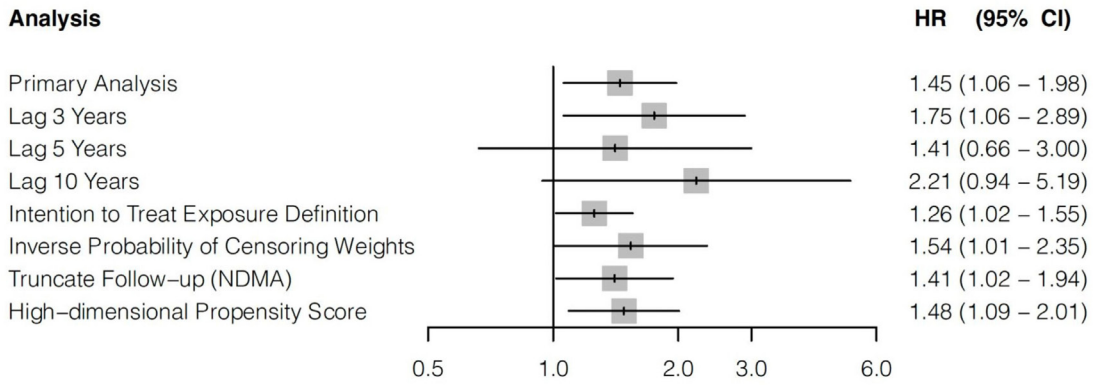

Figure 3 Forest plot summarising the results of primary and sensitivity analyses, with weighted HRs and 95% CIs for the association between use of proton pump inhibitors and gastric cancer, compared with the use of histamine-2 receptor antagonists. NDMA: N-Nitrosodimethylamine.

gastric cancer.[52 53] Thus, our study represents an important addition by minimising potential confounding by indication through the use of an active comparator. Beyond this, there were other significant limitations in previous studies, such as the inclusion of prevalent users,[9 10 17] which may have introduced survival bias and confounding,[54] important time-related biases[9–11 14–16 20] such as immortal-time bias and time-window bias,[23–25] and failure to account for cancer latency.[11 13] In this context, these conclusion-altering biases can lead to spurious and exaggerated associations, limiting the conclusions drawn from previous studies. We attempted to address these limitations through careful study design and numerous sensitivity analyses.

An association between PPI use and gastric cancer is biologically plausible and may be mediated by several different factors. PPIs are known to cause hypergastrinaemia (elevated secretion of gastrin from G-cells), as gastrin secretion is inhibited by acidity.[21] Gastrin is considered a potent growth factor, which may induce hyperplasia.[22] Second, long-term PPI use may lead to changes in the gut microbiome, including reduced microbial diversity.[55 56] Changes to the gut microbiota have been shown to contribute to an increased risk of gastric cancer.[57] Third, although disputed, chronic suppression of acid secretion by PPIs may be associated with atrophic gastritis (chronic inflammation of the stomach mucous membrane),[58 59] which is one of the main precursors to gastric cancer[60]; although not all studies have reported this association.[61] Taken together, these factors may contribute to gastric cancer development among PPI users. Finally, given that H2RAs decrease acid suppression by blocking the effects of histamine only, they are less effective than PPIs,[6] and are associated with lower gastrin levels (ie, less likely to induce hypergastrinaemia).[21] Thus, from a theoretical biological perspective, H2RAs are less likely to be associated with an increased risk of gastric cancer than PPIs.

Strengths and limitations of this study

This study has several strengths. First, to our knowledge, this is the largest study with the longest follow-up period conducted to date. Given the number of gastric events observed in our cohort, this study was sufficiently powered to address the long-term safety of PPIs and assess the risk among important subgroups, including by duration of use. Second, we restricted the cohort to new drug users, eliminating biases associated with the inclusion of prevalent users.[54] Third, the comparator group consisted of patients prescribed H2RAs, an active comparator that likely minimised confounding by indication. Moreover, the use of propensity score-weighted methods ensured an excellent balance of all baseline confounders. Finally, our results remained highly consistent across several sensitivity analyses.

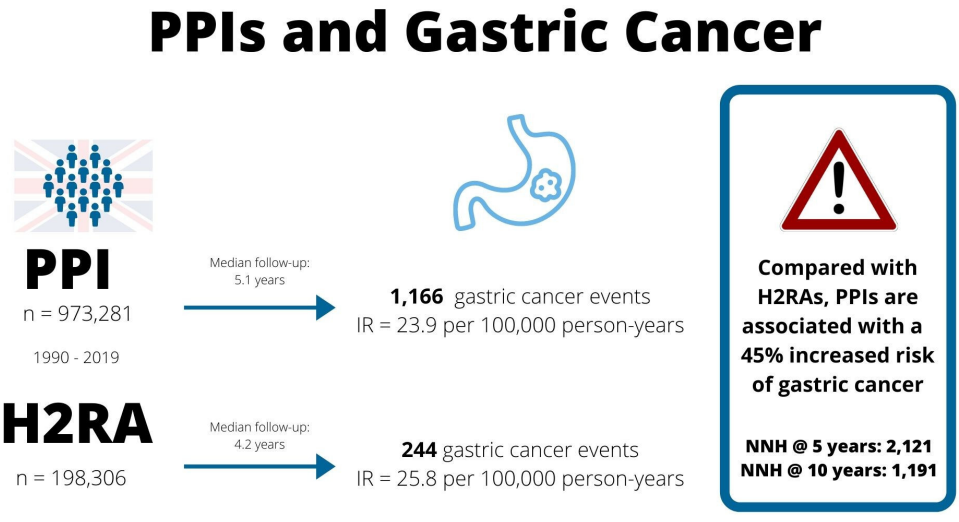

Figure 4 Graphical summary highlighting the main findings of the association between the use of proton pump inhibitors (PPIs) and gastric cancer, compared with the use of histamine-2 receptor antagonists (H2RA). IR, incidence rate; NNH, number needed to harm.

This study also has some limitations. First, prescriptions in the CPRD are written by general practitioners and not specialists, which may lead to some exposure misclassification. However, in the UK, general practitioners are responsible for the long-term care of most chronic conditions, including gastric disorders[62]; thus, we expect this misclassification to have been minimal. Similarly, it was not possible to directly assess treatment adherence, although this possible source of exposure misclassification is unlikely to be differential between the exposure groups. Second, PPIs and H2RAs are available over the counter in the UK, potentially leading to some missing prescription information. However, there is a financial incentive for patients requiring long-term PPI or H2RA use to receive prescriptions from their general practitioner rather than purchasing drugs over the counter. Third, it was not possible to stratify on the gastric cancer type (cardia vs non-cardia) as this information is not consistently recorded in the CPRD. Fourth, some secondary analyses may be underpowered, and should not be overinterpreted. Finally, given the observational nature of this study, residual confounding remains possible. While confounding from calendar time explained most of the observed difference between the crude and adjusted estimates,[4 42] we cannot rule out the potential impact of confounding from unmeasured or unknown confounders, including race and ethnicity. Moreover, there may be some residual confounding from imperfectly captured covariates, like *H. pylori* infection, which is not routinely tested for by general practitioners. Reassuringly, results from the HD-PS model, which considered an additional 200 empirically selected covariates, which may be proxies for unknown or unmeasured confounders,[63] were highly consistent with the primary analysis. Moreover, given the strength of the observed association, a post-hoc analysis showed that any unmeasured confounder would need to be strongly associated with both the exposure and outcome to nullify the observed results.

In summary, the results of this large real-world study suggest that patients newly treated with PPIs may be at an increased risk of gastric cancer compared with patients newly treated with H2RAs, although the absolute risk remains low. While PPIs have established clinical benefits when used according to evidence-based guidelines, this study highlights the need for physicians to regularly reassess the necessity of ongoing treatment. This is especially important in patients who are prescribed PPIs in the long term and for patients without an evidence-based indication for use.

Acknowledgements DA is the recipient of a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research. EGM holds a Chercheur-Boursier award from the Fonds de Recherche du Québec-Santé. MES holds a New Investigator Salary Award from the Canadian Institutes of Health Research and is the recipient of the Canadian Institutes of Health Research Canada Research Chair, Tier 2. SS is the recipient of the Distinguished James McGill Professorship award. LA holds a Chercheur-Boursier Senior award from the Fonds de Recherche du Québec-Santé and is the recipient of a William Dawson Scholar Award from McGill University.

Contributors All authors conceived and designed the study. LA acquired the data. DA and LA did the statistical analyses. MES and SS provided statistical expertise. All authors analysed and interpreted the data. EGM and ANB provided clinical expertise. DA wrote the manuscript, and all authors critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work. LA supervised the study and is the guarantor.

Funding Foundation Scheme grant from the Canadian Institutes of Health Research (FDN-143328).

Competing interests SS participated in advisory meetings or as a guest speaker for Atara Biotherapeutics, Boehringer-Ingelheim, Bristol-Myers-Squibb, Merck and Pfizer, all unrelated to this study. LA served as a consultant for Janssen and Pfizer for work unrelated to this study. The other authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 20_076) and by the Research Ethics Board of the Jewish General Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No additional data available.

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Supplementary Table 1. List of British National Formulary Codes for Proton Pump Inhibitors

British National Formulary Code	British National Formulary Header
01030500/05010103	Proton Pump Inhibitors/Broad-spectrum Penicillins
01030500/10010100	Proton Pump Inhibitors/Non-steroidal Anti-inflammatory Drugs
01030500/05010500	Proton Pump Inhibitors/Macrolides
1030500	Proton Pump Inhibitors

Supplementary Table 2. List of British National Formulary Codes for Histamine-2 Receptor Antagonists

British National Formulary Code	British National Formulary Header
1030100	H2 receptor antagonists
01030100/01010201	H2 receptor antagonists/Alginate preparations
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030100/01010202	H2 receptor antagonists/Indigestion remedies
01010201/01030100	Compound Alginate Preparations/H2-Receptor Antagonists
01010202/01030100	Indigestion Preparations/H2-Receptor Antagonists

Abbreviations: H2, Histamine-2.

Supplementary Table 3. Gastric Cancer Read Codes Used to Define Events

Read Code	Read Term
B11y100	Malignant neoplasm of posterior wall of stomach NEC
B11y000	Malignant neoplasm of anterior wall of stomach NEC
B110000	Malignant neoplasm of cardiac orifice of stomach
B11..11	Gastric neoplasm
B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
B110111	Malignant neoplasm of gastro-oesophageal junction
B113.00	Malignant neoplasm of fundus of stomach
B111.00	Malignant neoplasm of pylorus of stomach
B117.00	Malignant neoplasm, overlapping lesion of stomach
B11..00	Malignant neoplasm of stomach
B11yz00	Malignant neoplasm of other specified site of stomach NOS
B11y.00	Malignant neoplasm of other specified site of stomach
B11z.00	Malignant neoplasm of stomach NOS
B115.00	Malignant neoplasm of lesser curve of stomach unspecified
B116.00	Malignant neoplasm of greater curve of stomach unspecified
B114.00	Malignant neoplasm of body of stomach
B111000	Malignant neoplasm of prepylorus of stomach
B112.00	Malignant neoplasm of pyloric antrum of stomach
B110.00	Malignant neoplasm of cardia of stomach
B111100	Malignant neoplasm of pyloric canal of stomach
B111z00	Malignant neoplasm of pylorus of stomach NOS
B110z00	Malignant neoplasm of cardia of stomach NOS

Abbreviations: NEC, Neuroendocrine carcinoma; NOS, not otherwise specified.

Supplementary Table 4. Defined Daily Dose of Proton Pump Inhibitors

Proton Pump Inhibitor Type	Defined Daily Dose*
Omeprazole	20 mg
Esomeprazole	30 mg
Rabeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg

*All doses are equivalent to 1 Defined Daily Dose.

The dose of each PPI prescription was defined according to the World Health Organization defined daily dose and converted into omeprazole equivalents.[1] This allows for PPIs with different potencies to be compared. According to the defined daily dose, a patient prescribed a 30-day course of 30-mg of esomeprazole is equivalent to a patient prescribed a 30-day course of 20-mg omeprazole.

Supplementary Table 5. Crude and Adjusted HRs for the Association Between the Use of Specific Types of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists

Exposure	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonists	244	947,418	25.8 (22.6 to 29.2)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor type ‡						
Esomeprazole	17	78,412	21.7 (12.6 to 34.7)	0.86	1.15 (0.70 to 1.89)	1.25 (0.72 to 2.16)
Lansoprazole	426	1,685,920	25.3 (22.9 to 27.8)	0.98	1.37 (1.15 to 1.63)	1.48 (1.10 to 2.01)
Omeprazole	661	2,867,210	23.1 (21.3 to 24.9)	0.88	1.34 (1.13 to 1.58)	1.45 (1.03 to 2.02)
Pantoprazole	22	102,816	21.4 (13.4 to 32.4)	0.86	1.10 (0.71 to 1.71)	1.19 (0.73 to 1.95)
Rabeprazole	40	150,378	26.6 (19.0 to 36.2)	1.07	1.34 (0.95 to 1.89)	1.44 (0.96 to 2.15)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights.

‡ Combination users contributed 0 events and 3,035 person-years of follow-up.

Supplementary Table 6. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Age)

	Age < 65	**Age 65-74**	**Age ≥ 75**
Events	431	491	488
Person-Years	3,907,039	1,191,102	737,049
Crude incidence rate (95% CI) *	11.0 (10.0 to 12.1)	41.2 (37.7 to 45.0)	66.2 (60.5 to 72.4)
Crude HR			
Histamine-2 receptor antagonists	1.00	1.00	1.00
Proton pump inhibitors	0.77	1.02	1.00
			p-interaction: 0.18
Adjusted HR (95% CI) †			
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.27 (0.69 to 2.33)	1.42 (0.84 to 2.40)	1.71 (1.04 to 2.81)
			p-interaction: 0.75

Abbreviations: HR, hazard ratio; CI, confidence interval.
* Per 100,000 person-years.
†Weighted using standardized mortality ratio weights.

Supplementary Table 7. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Sex)

	Male	**Female**
Events	854	556
Person-Years	2,591,410	3,243,779
Crude Incidence Rate (95% CI)[*]	33.0 (30.8 to 35.2)	17.1 (15.7 to 18.6)
Crude HR		
Histamine-2 receptor antagonists	1.00	1.00
Proton pump inhibitors	0.87	0.98
		p-interaction: 0.43
Adjusted HR (95% CI)[†]		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.25 (0.84 to 1.88)	1.91 (1.22 to 3.00)
		p-interaction: 0.17

Abbreviations: HR, hazard ratio; CI, confidence interval.

[*] Per 100,000 person-years.

[†]Weighted using standardized mortality ratio weights.

Supplementary Table 8. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists Stratified by Approved Indication at Baseline

Indication *	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
Gastroesophageal reflux disease						
Histamine-2 receptor antagonists	20	78,410	25.5 (15.6 to 39.4)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	106	484,578	21.9 (17.9 to 26.5)	0.86	1.23 (0.71 to 2.13)	1.38 (0.59 to 3.22)
Peptic ulcer disease						
Histamine-2 receptor antagonists	21	40,570	51.8 (32.0 to 79.1)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	90	161,650	55.7 (44.8 to 68.4)	1.06	1.38 (0.77 to 2.48)	1.53 (0.48 to 4.92)
Dyspepsia						
Histamine-2 receptor antagonists	97	292,664	33.1 (26.9 to 40.4)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	270	954,590	28.3 (25.0 to 31.9)	0.86	1.19 (0.90 to 1.56)	1.12 (0.69 to 1.85)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Barrett's esophagus and *H. pylori* generated few events with unstable estimates.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 9. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists Stratified by Category of Calendar Year

Calendar Year	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
1990-1994					
Histamine-2 receptor antagonists	88	221,998	39.6 (31.8 to 48.8)	1.00	1.00 [Reference]
Proton pump inhibitor	21	61,313	34.3 (21.2 to 52.4)	0.89	0.95 (0.58 to 1.56)
1995-1999					
Histamine-2 receptor antagonists	83	282,105	29.4 (23.4 to 36.5)	1.00	1.00 [Reference]
Proton pump inhibitor	89	305,308	29.2 (23.4 to 35.9)	1.06	1.07 (0.78 to 1.46)
2000-2004					
Histamine-2 receptor antagonists	54	280,498	19.3 (14.5 to 25.1)	1.00	1.00 [Reference]
Proton pump inhibitor	315	1,143,684	27.5 (24.6 to 30.8)	1.57	1.43 (1.04 to 1.98)
2005-2009					
Histamine-2 receptor antagonists	9	114,596	7.9 (3.6 to 14.9)	1.00	1.00 [Reference]
Proton pump inhibitor	515	1,999,341	25.8 (23.6 to 28.0)	3.43	2.55 (1.21 to 5.38)
2010-2018					
Histamine-2 receptor antagonists	10	48,221	20.7 (9.9 to 38.1)	1.00	1.00 [Reference]
Proton pump inhibitor	226	1,378,125	16.4 (14.3 to 18.7)	0.82	0.87 (0.45 to 1.71)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights.

Supplementary Table 10. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Different Lag Periods)

Length of Lag Period	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
3 years						
Histamine-2 receptor antagonists	136	649,219	20.9 (17.6 to 24.8)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	671	3,235,785	20.7 (19.2 to 22.4)	0.99	1.28 (1.05 to 1.56)	1.75 (1.06 to 2.89)
5 years						
Histamine-2 receptor antagonists	102	441,939	23.1 (18.8 to 28.0)	1.00	1.00	1.00 [Reference]
Proton pump inhibitors	435	2,047,297	21.2 (19.3 to 23.3)	0.91	1.21 (0.96 to 1.52)	1.41 (0.66 to 3.00)
10 years						
Histamine-2 receptor antagonists	36	36,462	24.4 (17.1 to 33.8)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	95	490,853	19.4 (15.7 to 23.7)	0.78	1.00 (0.67 to 1.49)	2.21(0.94 to 5.19)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights.

Supplementary Table 11. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Intention-to-treat Exposure Definition) *

Exposure	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonists	493	1,760,954	28.0 (25.6 to 30.6)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1,256	5,275,112	23.8 (22.5 to 25.2)	0.82	1.12 (0.99 to 1.26)	1.26 (1.02 to 1.55)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Did not censor on switch from PPI to H2RA or H2RA to PPI.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 12. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Adjustment for IPCW)

Exposure	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonists	244	1,253,913	19.5 (17.1 to 22.1)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1,166	6,360,764	18.3 (17.3 to 19.4)	0.93	1.41 (1.20 to 1.66)	1.54 (1.01 to 2.35)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights and inverse probability of censoring weights for death and switching.

Supplementary Table 13. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Truncate Follow-up for Possible NDMA Contaminant)*

Exposure	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonists	243	932,052	26.1 (22.9 to 29.6)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1,113	4,497,921	24.7 (23.3 to 26.2)	0.94	1.33 (1.14 to 1.56)	1.41 (1.02 to 1.94)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Follow-up truncated on December 31, 2017.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 14. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (HD-PS)*

Exposure	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonists	244	947,396	25.8 (22.6 to 29.2)	1.00	1.00 [Reference]
Proton pump inhibitors	1,166	4,887,522	23.9 (22.5 to 25.3)	0.92	1.48 (1.09 to 2.01)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Treatment weights created using predefined covariates listed in the manuscript and 200 empirically selected covariates from the HD-PS algorithm.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 15. Sensitivity Analysis Without Assumptions for Unmeasured Confounding

Risk ratio for unmeasured confounder and exposure association	Risk ratio for unmeasured confounder and outcome association								
	1.2	**1.3**	**1.5**	**1.8**	**2.0**	**2.5**	**3.0**	**4.0**	**5.0**
1.2	1.41 (1.03-1.93)	1.39 (1.02-1.90)	1.37 (1.00-1.87)	1.34 (0.98-1.83)	1.33 (0.97-1.82)	1.31 (0.95-1.78)	1.29 (0.94-1.76)	1.27 (0.93-1.73)	1.26 (0.92-1.72)
1.3	1.39 (1.02-1.9)	1.37 (1.00-1.87)	1.34 (0.98-1.83)	1.3 (0.95-1.78)	1.28 (0.94-1.75)	1.25 (0.91-1.71)	1.23 (0.9-1.68)	1.20 (0.88-1.64)	1.18 (0.86-1.61)
1.5	1.37 (1.00-1.87)	1.34 (0.98-1.83)	1.29 (0.94-1.76)	1.24 (0.90-1.69)	1.21 (0.88-1.65)	1.16 (0.85-1.58)	1.13 (0.82-1.54)	1.09 (0.80-1.49)	1.06 (0.78-1.45)
1.8	1.34 (0.98-1.83)	1.3 (0.95-1.78)	1.24 (0.90-1.69)	1.16 (0.85-1.59)	1.13 (0.82-1.54)	1.06 (0.78-1.45)	1.02 (0.75-1.39)	0.97 (0.71-1.32)	0.93 (0.68-1.28)
2.0	1.33 (0.97-1.82)	1.28 (0.94-1.75)	1.21 (0.88-1.65)	1.13 (0.82-1.54)	1.09 (0.80-1.49)	1.02 (0.74-1.39)	0.97 (0.71-1.32)	0.91 (0.66-1.24)	0.87 (0.64-1.19)
2.5	1.31 (0.95-1.78)	1.25 (0.91-1.71)	1.16 (0.85-1.58)	1.06 (0.78-1.45)	1.02 (0.74-1.39)	0.93 (0.68-1.27)	0.87 (0.64-1.19)	0.80 (0.58-1.09)	0.75 (0.55-1.03)
3.0	1.29 (0.94-1.76)	1.23 (0.90-1.68)	1.13 (0.82-1.54)	1.02 (0.75-1.39)	0.97 (0.71-1.32)	0.87 (0.64-1.19)	0.81 (0.59-1.1)	0.73 (0.53-0.99)	0.68 (0.49-0.92)
4.0	1.27 (0.93-1.73)	1.20 (0.88-1.64)	1.09 (0.80-1.49)	0.97 (0.71-1.32)	0.91 (0.66-1.24)	0.8 (0.58-1.09)	0.73 (0.53-0.99)	0.63 (0.46-0.87)	0.58 (0.42-0.79)
5.0	1.26 (0.92-1.72)	1.18 (0.86-1.61)	1.06 (0.78-1.45)	0.93 (0.68-1.28)	0.87 (0.64-1.19)	0.75 (0.55-1.03)	0.68 (0.49-0.92)	0.58 (0.42-0.79)	0.52 (0.38-0.71)

Supplementary Method 1. Inverse Probability of Censoring Weights

We used inverse probability of censoring weighting to assess the potential impact of differential censoring from drug switching (i.e. PPI users adding-on/switching to H2RAs, and vice versa) (1, 2), and to investigate death as a competing risk between PPI and H2RA users (3). This analysis was completed in three steps.

Step 1:

For both exposure groups, the follow-up period will be sudivided into one-year intervals. Inverse probability of censoring weights (IPCWs) were fit using logistic regression to predict the probability of remaining uncensored (i.e. not switching or adding on from PPI to H2RA and vice versa) at a given interval, conditional on the following variables, all measured in the previous interval: age, sex, alcohol related disorders (alcohol dependency, alcoholic cirrhosis of the liver, alcoholic hepatitis, hepatic failure), smoking status (current, former, never, unknown), body mass index, atrial fibrillation, anemia, cancer (excluding non-melanoma skin cancer), congestive heart failure, gastric metaplasia, hypercholesterolemia, hypertension, venous thromboembolism, chronic kidney disease, stroke, hernia, gastrointestinal bleeding, dialysis, gastric surgery, indications for acid suppressant drug use (approved indications: Barrett's esophagus, *Helicobacter pylori* infection, gastro-oesophageal reflux disease, peptic ulcer disease, dyspepsia; off-label indications: gastritis/duodenitis and stomach pain) and use of the following medications: metformin, non-steroidal anti-inflammatory drugs, antiplatelets, dual antiplatelets, cyclooxygenase-2 inhibitors, synthetic prostaglandin analogs, selective serotonin reuptake inhibitors, anticoagulants and steroids.

Step 2: We repeated step 1 by fitting a logistic regression model for remaining alive at a given interval (i.e. not having death as a competing event), using the same covariates as above.

Step 3: Using the fitted logistic models generated in Steps 1 and 2, we took the product of the weights (i.e. inverse of the probability of being uncensored from drug switching and from not dying) across all intervals for a given patient. We then stabilized the weight for each patient using intercept only models as the numerator. Unstable weights were truncated at the 0.5^{th} and 99.5^{th} percentile. For each patient, the stabilized IPCWs generated in steps 1 and 2 were multiplied along with the standardized mortality ratio weights used in the primary model to generate an overall weight. Thus, stabilized IPCWs and treatment weights were used to estimate the marginal hazard ratio of gastric cancer associated with the use of PPIs compared with H2RAs.

Supplementary Method 2. High-dimensional propensity-scores

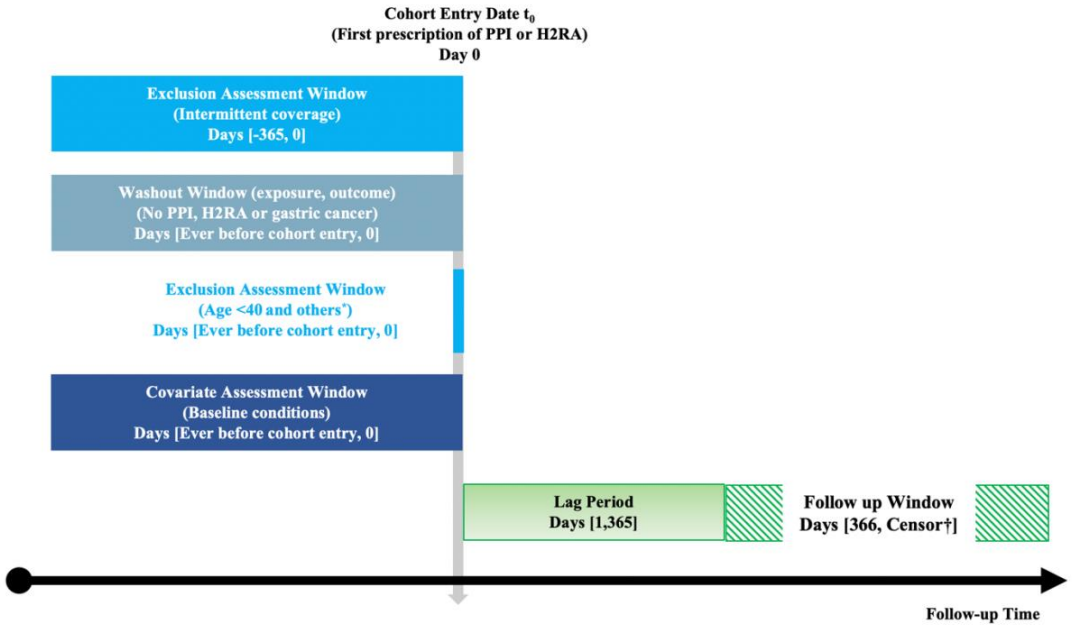
We used the high-dimensional propensity score (HD-PS) approach to reweigh our study population to investigate the impact of residual confounding. The HD-PS is a seven-step algorithm which empirically selects covariates from different data dimensions based on their prevalence and potential for confounding (4). The HD-PS represents an efficient means to control for confounding as adjustment is based on this summary score and not individual covariate values. The HD-PS model may also account for some unmeasured confounding, as the empirically selected variables may include proxies for unmeasured or unknown confounders (5).

Using the HD-PS algorithm, we empirically selected 200 covariates, in addition to the prespecified covariates listen in the manuscript and calendar year of cohort entry. Covariates were selected from five data dimensions, including prescriptions, procedures, diagnoses, disease history and administrative files. Propensity scores were then estimated using logistic regression as the predicted probability of receiving a PPI versus a H2RA, conditional on the empirically selected covariates, predefined covariates listed in the manuscript and calendar year of cohort entry. Using the estimated predicted probabilities, we reweighed the cohort using standardized mortality ratio weighting.(6) Patients exposed to PPIs were given a weight of 1, and patients exposed to H2RAs were given a weight of the odds of treatment probability (PS/[1-PS]) (6). Treatment weights were combined with IPCWs, and marginal hazard ratios for gastric cancer for users of PPIs compared to users of H2RAs were estimated.

Supplementary Method 3. Sensitivity analysis without assumptions

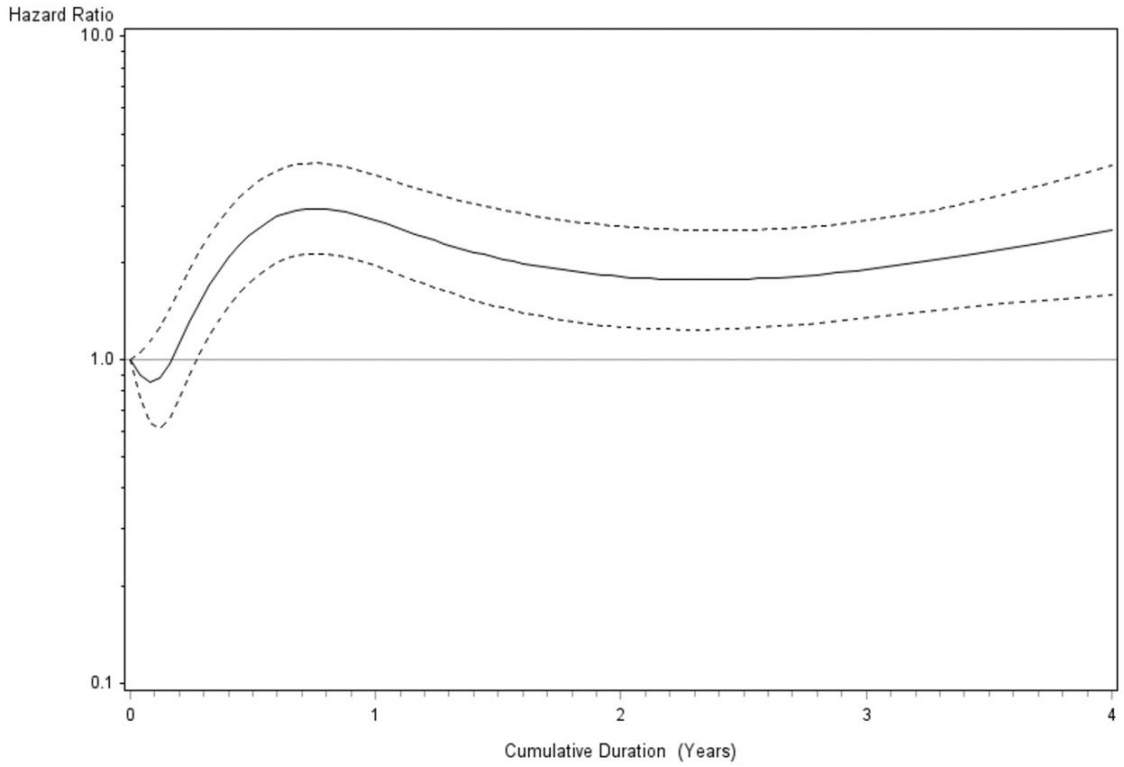
To assess the impact of residual confounding on the observed hazard ratio, we conducted a post-hoc sensitivity analysis using the model proposed by Ding and VanderWeele (7). This model is a flexible approach to dealing with unmeasured confounding as it does not impose assumptions on the unmeasured confounder(s). Instead, the model derives a joint bounding factor and a sharp inequality. For an unmeasured confounder to explain away the observed hazard ratio, the sensitivity analysis parameters must satisfy the inequality. Thus, to nullify the observed hazard ratio observed in this study (HR: 1.45, 95% CI: 1.06 – 1.98), an unmeasured confounder would need to be strongly associated with both the exposure and the outcome (supplementary table 17). Should the strength of the association between an unmeasured confounder and the outcome have a magnitude of 3.0, this confounder would also need to be associated with the exposure to a magnitude of 2.0 to nullify the observed hazard ratio.

Supplementary Figure 1. Cohort Construction



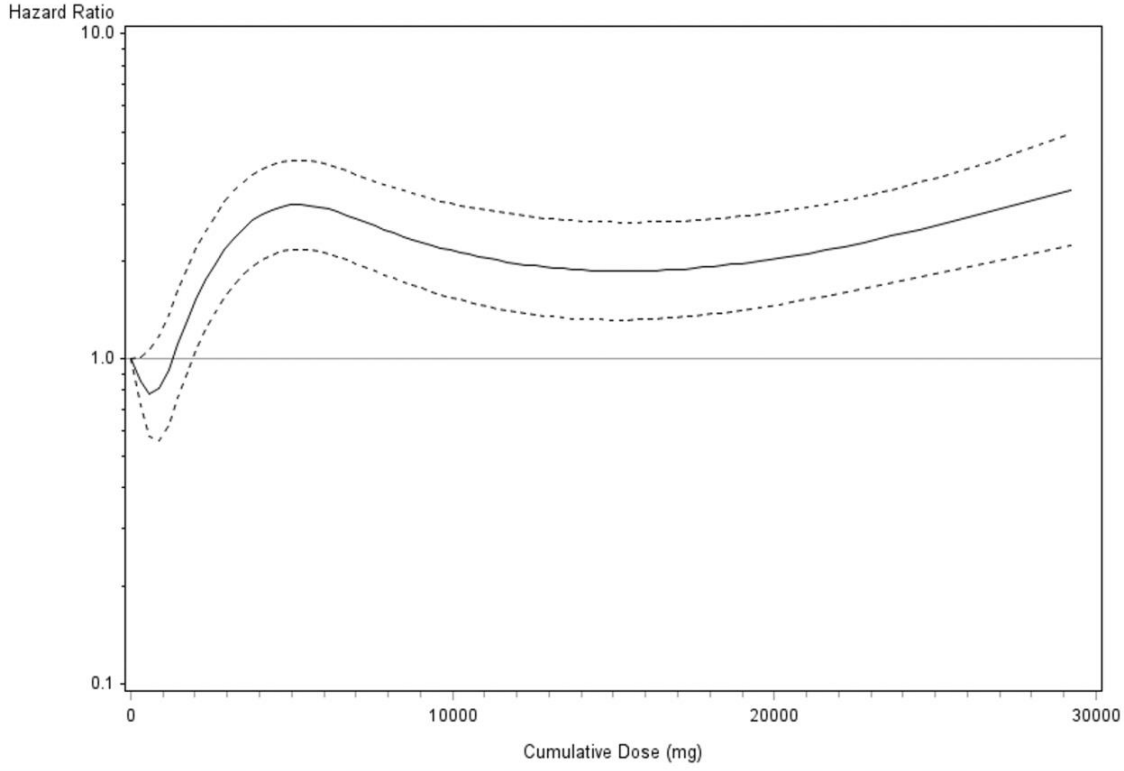
* Concomitant PPI and H2RA use, inherited cancer syndromes, less than 1 year of follow-up.
† Earliest of an incident diagnosis of gastric cancer, death from any cause, 1 year after switch between study drugs, end of registration, last collection date, or end of the study period (April 30, 2019), whichever occurs first.
Abbreviations: PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist.

Supplementary Figure 2. Restricted Cubic Spline of Cumulative Duration of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve using 5 knots of weighted hazard ratio of gastric cancer disease (solid line) and 95% confidence limits (dashed lines) as function of cumulative duration of proton pump inhibitor use. Cumulative duration was truncated at 4 years of use because of few events.

Supplementary Figure 3. Restricted Cubic Spline of Cumulative Dose of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve using 5 knots of weighted hazard ratio of gastric cancer disease (solid line) and 95% confidence limits (dashed lines) as function of cumulative dose of proton pump inhibitor use. Cumulative dose was truncated at 29,200 mg of use, which is equivalent to 4 years of daily omeprazole 20 mg, because of few events.

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