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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

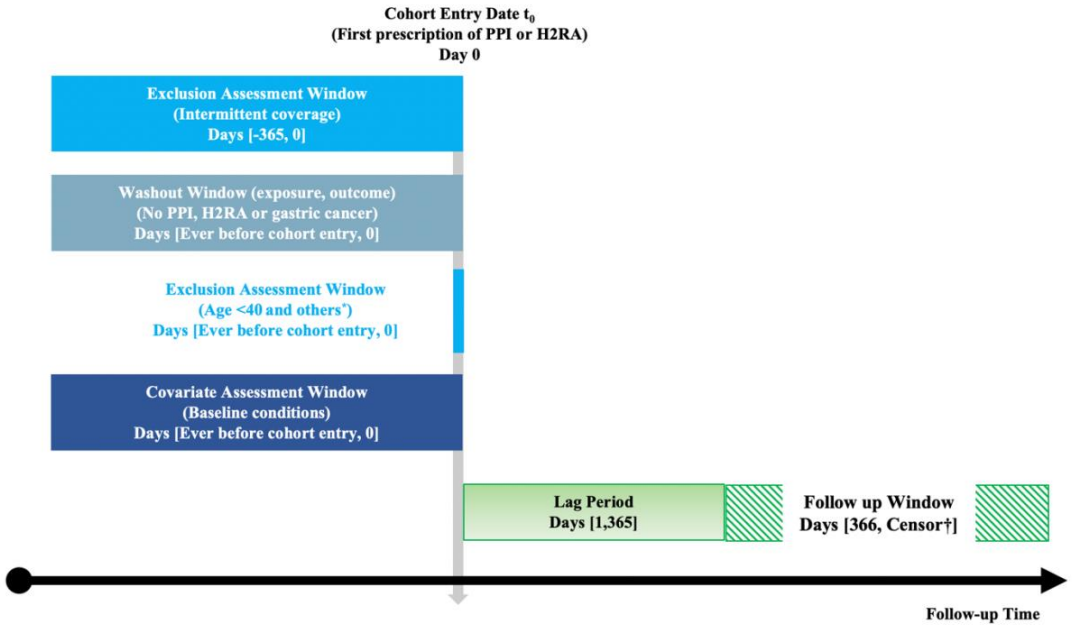
We used the high-dimensional propensity score (HD-PS) approach to reweigh our study population to investigate the impact of residual confounding. The HD-PS is a seven-step algorithm which empirically selects covariates from different data dimensions based on their prevalence and potential for confounding (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

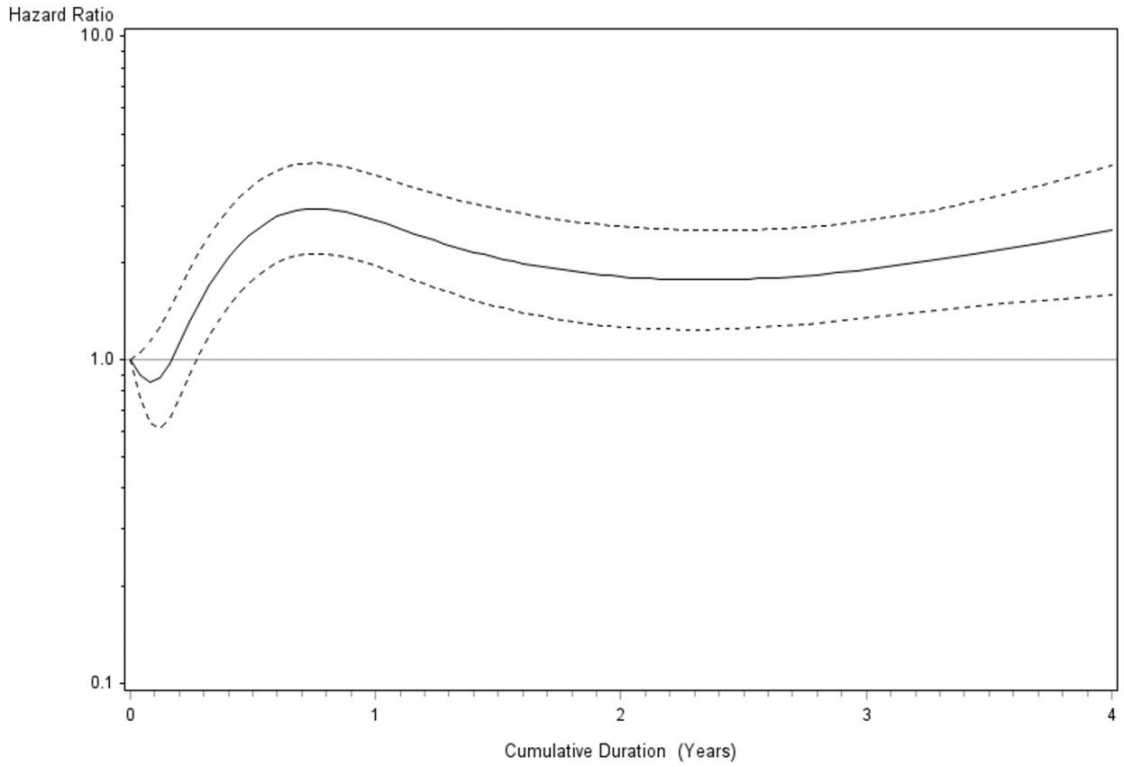
To assess the impact of residual confounding on the observed hazard ratio, we conducted a post-hoc sensitivity analysis using the model proposed by Ding and VanderWeele (7). This model is a flexible approach to dealing with unmeasured confounding as it does not impose assumptions on the unmeasured confounder(s). 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



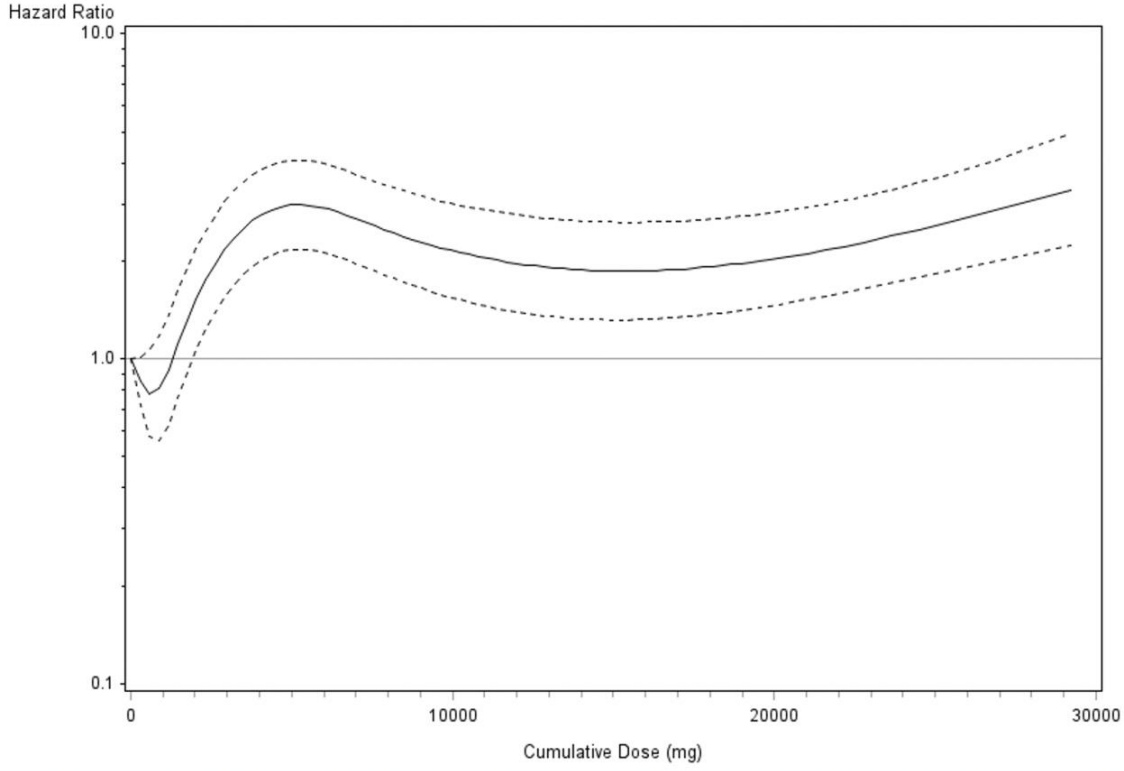
* Concomitant PPI and H2RA use, inherited cancer syndromes, less than 1 year of follow-up.
† Earliest of an incident diagnosis of gastric cancer, death from any cause, 1 year after switch between study drugs, end of registration, last collection date, or end of the study period (April 30, 2019), whichever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