Title: Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies.

Short title: Acid-suppressing therapies and liver cancer.

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STRUCTURED SUMMARY

Background & Aims

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are commonly used. PPIs have been shown to promote liver cancer in rats; however, only one study has examined the association in humans. We investigated PPIs and H2RAs and risk of primary liver cancer in two large independent study populations.

Methods

We conducted a nested case-control study within the Primary Care Clinical Informatics Unit (PCCIU) database in which up to five controls were matched to cases with primary liver cancer, recorded by General Practitioners. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations with prescribed PPIs and H2RAs were calculated using conditional logistic regression. We also conducted a prospective cohort study within the UK Biobank using self-reported medication use and cancer-registry recorded primary liver cancer. Hazard ratios (HRs) and 95% CIs were calculated using Cox regression.

Results

In the PCCIU case-control analysis, 434 liver cancer cases were matched to 2,103 controls. In the UK Biobank cohort, 182 out of 475,768 participants developed liver cancer. In both, ever use of PPIs was associated with increased liver cancer risk (adjusted OR 1.80, 95% CI 1.34, 2.41 and adjusted HR 1.99, 95% CI 1.34, 2.94, respectively). There was little evidence of association with H2RA use (adjusted OR 1.21, 95% CI 0.84, 1.76 and adjusted HR 1.70, 95% CI 0.82, 3.53, respectively).

Conclusion

We found some evidence that PPI use was associated with liver cancer. Whether this association is causal or reflects residual confounding or reverse causation requires additional research.

Keywords: proton pump inhibitors, histamine-2 receptor antagonists, hepatocellular carcinoma, intrahepatic bile duct carcinoma, cohort, case-control.

INTRODUCTION

Primary liver cancer is the fifth most common cancer in men and ninth in women in the world[1]. Recently the incidence and mortality from liver cancer has increased markedly both in the UK[2] and US[3]. The low estimates of five year relative survival of 15% in the US[4], and 8% in the UK[5], highlight the importance of preventing liver cancer.

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are widely prescribed medications, used primarily for the treatment of peptic ulcers, dyspepsia, and gastro-oesophageal reflux disease (GORD). Despite their widespread use, there have been concerns about potential adverse effects of PPIs[6,7] and H2RAs[8] potentially caused by a range of mechanisms including the reduced absorption of nutrients[9] , hypergastrinemia[10] and the overgrowth of bacteria (due to lower stomach acid levels)[8,11]. Many studies have investigated the effect of PPIs and H2RAs on the stomach[12,13], and particularly on gastric cancer risk[14,15]. Recently additional concerns have been raised about the effects that PPIs and H2RAs have upon the liver. A recent animal study found that PPIs promote progression of alcoholic liver disease, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis in mice[16] due to an overgrowth of bacteria. Likewise, in another animal study, PPI use was shown to promote liver tumors in rats[17].

Despite these findings, only one previous observational study has examined the association between PPI and H2RA use and the risk of primary liver cancer in humans[18]. That case-control study, which only investigated hepatocellular carcinoma (HCC), and not intrahepatic bile duct carcinoma (IBDC), observed a marked increase in risk of HCC with H2RA use but not PPI use. We therefore examined the

association between use of PPIs and H2RAs and the risk of primary liver cancer using data from two independent UK datasets.

MATERIALS and METHODS

Primary Care Clinical Informatics Unit (PCCIU)

Data source

The Primary Care Clinical Informatics Unit (PCCIU) database is an electronic primary care dataset from Scotland that captures approximately 15% of the Scottish population[19]. The PCCIU contains computerized medical records containing data from 1993 and 2011 capturing approximately 15% of the Scottish general practice population. The PCCIU contains demographics and details of patient encounters, clinical diagnosis, and prescriptions. Data access was approved by the Research Applications and Data Management Team of the University of Aberdeen, and we obtained ethics approval for this analysis from the School of Medicine, Dentistry and Biomedical Sciences Research Ethics Committee at Queen's University Belfast (reference number: 15.43)

Study design

We conducted a nested case-control study within PCCIU. Cases had a first diagnosis of primary liver cancer, including HCC and IBDC, (based upon GP Read code: B15, excluding B153) between January 1, 1999 and April 30, 2011. Up to five controls were matched to each case on exact year of birth, sex and General Practitioners (GP) practice. The index date for the cases was defined as the date of diagnosis of primary liver cancer and cases had to be free from cancer (excluding non-melanoma skin

cancer) prior to this date. The index date for the controls was the diagnosis date of their matched case, controls were free from any cancer (apart from non-melanoma skin cancer) prior to the index date.

The start of prescription records was considered January 1, 1996 (as prescriptions prior to this date were less likely to have been electronically recorded) or the date of patient registration at a GP practice if this occurred after January 1, 1996. The shortest duration of available prescription records was determined within each matched set of a case and controls. The start of the exposure period was then set as the index date minus this duration within each matched set of a case and controls to ensure all members of the matched set had an identical length of exposure period. The end of the exposure period was one year prior to the index date to reduce the potential for reverse causation due to increased exposure to healthcare professionals following cancer symptoms. Cases and controls with less than three years of prescription records prior to their index date were excluded.

Exposure

Medication use was determined from GP prescriptions in the exposure period. For each case and control, we extracted prescriptions for PPIs[20] (including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole sodium) and H2RAs[20] (including cimetidine, famotidine, nizatidine, ranitidine). A quantity of 56 tablets was assumed for the less than 0.1% of prescriptions where the quantity recorded in the PCCIU database was assumed incorrect, based upon the most common PPI prescription size. Defined daily doses (DDD) were calculated from the quantity of tablets and strength, as defined by World Health Organization[21].

Covariates

Comorbidities were obtained from GP diagnosis codes prior to the index date, including diabetes, coronary heart disease, myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, cerebrovascular accident, chronic obstructive pulmonary disease, mental illness, gastro-oesophageal reflux disease, peptic ulcer disease, and liver diseases (hepatitis, cirrhosis, alcoholic fatty liver, non-alcoholic fatty liver, biliary cirrhosis). Statins and aspirin use were identified from prescription records. Lifestyle risk factors were extracted from GP records including smoking status (never smoker, previous smoker, and current smoker), alcohol status (none, low [e.g. moderate or light drinker], or high intake [e.g. above recommended limits, chronic alcoholism]), and obesity ([BMI>30], or not obese) using the most recent record prior to the index date. Postcode of the GP practice was used to assign deprivation fifths using the Scottish Index of Multiple Deprivation[22].

UK Biobank

Data source

The UK Biobank contains approximately 500,000 volunteer participants aged 40 to 69 from England, Scotland and Wales recruited from 2006 to 2010[23]. A wide range of data was collected including lifestyle, environment, medical history and physical measures, along with biological samples. The UK Biobank is linked to cancer registry data from the Health and Social Care Information Centre (in England and Wales) and the National Health Service Central Register (in Scotland). The UK Biobank has ethical approval from the North West Multi-Centre Research Ethics Committee. All participants provided written informed consent.

Study design

We conducted a prospective cohort study among participants in the UK Biobank. Liver cancer patients were identified using cancer registry records (based upon ICD 10 codes C22, liver and intrahepatic bile duct cancer) up to September 30, 2014. Participants with a cancer diagnosis (apart from non-melanoma skin cancer) prior to baseline or in the year after baseline were excluded (as these cancers may have been present at baseline). Consequently, cohort participants were followed from one year after baseline until the date of liver cancer diagnosis or censoring (on the earliest of the date of death, date of other cancer, or September 30, 2014).

Exposure

Self-reported PPI and H2RA use was first ascertained from participants using a touchscreen questionnaire at baseline, and then verified during verbal interview with a UK Biobank nurse.

Covariates

Covariates were determined from patient interview and touch screen at baseline. These included age, gender, comorbidities (gastro-oesophageal reflux disease, peptic ulcer disease, cirrhosis, hepatitis, and diabetes) and other medication use (statins and aspirin). Lifestyle risk factors including smoking (never smoker, previous smoker or current smoker) and alcohol consumption (never, <1 day per week, 1-2 days per week, 3-4 days per week or >4 days per week) were also ascertained. BMI (categorized as under or normal weight [<25], overweight [25-30], obese [>30]) was calculated from height and weight measurements recorded at baseline by trained research staff. The Townsend score based upon postcode of residence was determined as a measure of deprivation[24].

Statistical analysis

The characteristics of cases and control were compared using descriptive statistics (for continuous variables) or frequencies and percentages (for categorical variables).

In PCCIU, we used conditional logistic regression to estimate odd ratios (OR) and 95% confidence intervals (95% CI) for the association between PPI/H2RA use and liver cancer risk. The matched design accounted for age, sex and GP practice, and adjustments were made for comorbidities (as described), obesity, aspirin and statins use. A separate complete case analysis was conducted additionally adjusted for smoking and alcohol.

Analyses were repeated by number of prescriptions, by DDDs and by type of PPIs. Similar analyses were conducted for H2RA use. A sensitivity analysis was conducted adjusting for H2RAs and PPIs simultaneously. Additional sensitivity analyses were conducted removing prescriptions in the 2 years prior to index date (including only patients with 4 years of medical records), and in the 4 years prior to index date (including only patients with 6 years of medical records), to investigate the potential for reverse causation potentially due to gastrointestinal symptoms. A further sensitivity analysis was conducted adjusting for smoking and alcohol using multiple imputation with chained equations[25]. First, an imputation model was created using ordered logit models including age, gender, PPI, H2RA, obesity, comorbidity, statins and aspirin use, separately for cases and controls. Twenty-five imputations were conducted and results were combined using Rubin's rules[26].

The UK Biobank cohort was analysed using Cox regression with age as the underlying time scale (individuals were considered at risk from birth and under observation from age at baseline, left truncated) to calculate hazard ratios (HR) and 95% CIs for PPI/H2RA use and liver cancer risk and by

histological types (HCC based upon ICD 10 code C22.0 and IBDC code C22.1). In adjusted analyses the model contained age, gender, deprivation, BMI, alcohol, smoking, comorbidities at baseline (GORD, peptic ulcer disease, cirrhosis, hepatitis and diabetes) and statins and aspirin use at baseline. Sensitivity analyses were conducted adjusting for H2RAs and PPIs simultaneously and by repeating the analyses starting follow-up at 2 years and 4 years after baseline (to remove cancers within 2 and 4 years, respectively, which could have influenced medication prescribing at baseline).

RESULTS

PCCIU

Our nested case-control study in PCCIU included 434 cases of liver cancer and 2,103 matched controls (Table 1). The median exposure period was 5.5 years (min 2.0, max 13.3) in cases and controls. Liver cancer cases were more likely than controls to smoke, consume high levels of alcohol, use aspirin, and have diabetes, liver diseases and peptic ulcer.

Overall, a greater proportion of liver cancer cases used PPIs compared with controls (33% vs 23%) (Table 2). PPI use was associated with increased risk of liver cancer (unadjusted OR 1.74, 95% CI 1.38, 2.19; fully adjusted OR 1.80, 95% CI 1.34, 2.41). However, we found no evidence of a dose response relationship with increased duration of exposure (1-11 PPI prescriptions fully adjusted OR =1.92, 95% CI 1.33, 2.69 and 12 or more prescriptions OR =1.66, 95% CI 1.13, 2.45). Associations were similar when exposure was based upon DDDs. There were stronger associations for omeprazole (fully adjusted OR 1.83, 95% CI 1.30, 2.56) than lansoprazole (fully adjusted OR 1.34, 95% CI 0.93, 1.93).
We found no association between H2RA use and risk of liver cancer (ever H2RA use: fully adjusted OR 1.21, 95% CI 0.84, 1.76), regardless of duration of use and type (Table 2).

In sensitivity analyses (Table 3), the association with PPI use was moderately attenuated after introducing 2 year (fully adjusted OR 1.65, 95% CI 1.15, 2.35) and 4 year lags (fully adjusted OR 1.60, 95% CI 0.97, 2.64). Associations were similar in other sensitivity analyses.

UK Biobank

Among 471,851 participants in the UK Biobank, we identified 182 liver cancer cases over a median follow-up of 5.6 years (range 1.0-8.6 years). Liver cancer cases were more likely than controls to be older, male, from deprived areas, smoke, consume alcohol more often, be overweight or obese, have diabetes, cirrhosis, hepatitis, and use statins and aspirin (Table 1).

Ever use of PPIs was associated with 2-fold increased risk of liver cancer (unadjusted HR 2.08, 95% CI 1.46, 2.96; fully adjusted HR 1.99, 95% CI 1.34, 2.94). The magnitude of the association with PPI use was greater for risk of IBDC (adjusted HR 3.12, 95% CI 1.72, 5.68) than for risk of HCC (adjusted HR 1.60, 95% CI 0.91, 2.83). The associations were similar by type of PPIs. A similar, though not statistically significant, association was observed between H2RAs and liver cancer risk (adjusted HR 1.70; 95% CI 0.82, 3.53).

Sensitivity analyses (Table 5) revealed the association between PPI use and liver cancer was slightly attenuated after introducing a 2 year lag (adjusted HR 1.79, 95% CI 1.15, 2.77) and more attenuated when a 4 year lag was introduced (adjusted HR 1.30, 95% CI 0.66, 2.55). This pattern was similar for HCC and IBDC.

DISCUSSION

Using data from two large population-based studies which differed in design (case-control versus prospective cohort) and method of exposure ascertainment (self-report versus prescription records), we found a consistent association between PPI use and liver cancer risk. Conversely, there was little evidence of association with use of H2RAs. PPI use was more strongly associated with the risk of IBDC than for HCC, and the association was not attenuated after adjustments for available confounders. However the associations were slightly attenuated when controlling for potential reverse causation (using lags) and, using data from PCCIU, we found no evidence of a dose response based upon duration of use.

A previous case-control study in Taiwan[18] found a statistically significant association between use of H2RAs and the risk of HCC (adjusted OR 1.46 95% CI 1.30, 1.64) but not PPIs (adjusted OR 0.94, 95% CI 0.78, 1.13), but did not investigate IBDC. Although we observed stronger associations between PPIs and liver cancer risk, in analyses by subtype these associations were only apparent for IBDC. The difference in the findings of our study and the Taiwan study are unclear but could reflect differences in the underlying populations with respect to other liver cancer risk factors or genetic factors, differences in PPI prescribing patterns, or study specific differences (for instance they frequency matched controls to cases whereas we individually matched).

Our study has a number of strengths. We observed consistent findings for PPIs and liver cancer risk across two independent datasets. There was minimal risk of recall bias as PCCIU analyses were based upon GP prescription records whilst UK Biobank was a prospective cohort study in which medications

were recorded at least one year prior to liver cancer onset. In both datasets we adjusted for a wide range of confounders and, particularly, in UK Biobank we had detailed information on lifestyle risk factors including smoking and alcohol. Also, data on number of prescriptions were available in PCCIU.

The main limitation is that we cannot rule out confounding by incomplete or unknown exposures. Although we adjusted for cirrhosis and liver disease, cirrhosis patients are commonly prescribed PPIs[27] and therefore any misclassification within PCCIU or UK Biobank could lead to residual confounding. Furthermore we cannot rule out confounding by indication[28], for example, individuals with gastro-oesophageal reflux disease, for which they receive PPIs, have been shown to have increased risk of nonalcoholic fatty liver disease[29] which is a risk factor for primary liver cancer. There was an indication of reverse causation as the associations were slightly attenuated when medication use in the period prior to onset was removed, which could be influenced by liver cancer symptoms. A further weakness was that histological subtype was not available in PCCIU but we did have these data in UK Biobank. Finally, adherence to medications was unknown in either dataset, but this seems more likely to dilute associations.

The cause of the observed increased risk of liver cancer with PPIs use is unknown. If real, our findings are consistent with an experimental study which showed that PPIs can promote liver tumors in rats[17]. Various potentially harmful mechanisms of PPIs have been proposed[9]. In particular, long term PPIs use can lead to hypergastrinemia which has been shown to have a carcinogenic effect[30] , particularly on liver cells[31] . Also PPIs reduce gastric acid secretion increasing the survival of various microbes in the stomach[7,32]. The resulting bacterial overgrowth could greatly contribute to the transformation of primary bile acid in the intestine to secondary bile acid[33] and has been shown to impact upon the liver[34]

exacerbating various liver diseases in mice[16]. A high level of secondary bile acid has been shown to cause toxic, inflammatory, and DNA damaging effects on liver cells and bile duct cells, leading to HCC[35] and cholangiocarcinoma[36]. The generally weaker associations observed for H2RAs could reflect the weaker acid suppression and the less marked effect on gastrin associated with these medications[10]. Alternatively, various features of the observed association do not support a causal interpretation including the lack of dose response (the most marked association was seen for less than 6 prescriptions), the possibility of confounding by indication, and the possibility of reverse causation (suggested by the attenuation of associations when prescriptions in the period prior to diagnosis where removed). However, the widespread use of PPIs, and particularly their use without clear indication[37], and the high mortality of liver cancer highlight the need for further research. Specifically, further studies should contain sufficiently long follow-up to investigate reverse causation, high quality liver cancer outcome data and detailed and complete information on liver cancer risk factors.

In conclusion, our study provides some evidence of an association between PPI use and the risk of liver cancer; however, this association requires confirmation in other studies due to the possibility of residual confounding and/or reverse causation.

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Table1: Characteristics of liver cancer cases and controls in Primary Care Clinical Informatics Unit and UK Biobank

	Primary Care Clinical Informatics Unit		UK Biobank	
	Cases	Controls	Cases	Controls
Count	434 (17.1%)	2,103 (82.9%)	182	471669
Median exposure years	5.47	5.45		
(min, max)	(2.00, 13.31)	(2.00, 13.31)		
Year of diagnosis: 1996-1999	10 (2.3%)			
2000-2003	82 (18.9%)			
2004-2007	237 (54.6%)			
2008-2011	105 (24.1%)		67 (36.8%)	
2012-2015			115 (63.2%)	
Age at index[†]/baseline[†]:0-49	12 (2.8%)	61 (2.9%)	6 (3.3%)	114821 (24.3%)
50-59	62 (14.3%)	316 (15.0%)	59 (32.4%)	158665 (33.6%)
60-69	139 (32.0%)	693 (32.9%)	114 (62.6%)	196054 (41.6%)
70-79	143 (32.9%)	693 (32.9%)	3 (1.6%)	2129 (0.5%)
80+	78 (17.9%)	340 (16.2%)		
Male	292 (67.3%)	1412 (67.1%)	114 (62.6%)	217239 (46.1%)
Deprivation: 1 (Least deprived)	70 (16.1%)	340 (16.2%)	27 (14.8%)	94450 (20.0%)
2	61 (14.0%)	294 (14.0%)	35 (19.2%)	94030 (19.9%)
3	84 (19.4%)	413 (19.4%)	41 (22.5%)	93947 (19.9%)
4	105 (24.2%)	501 (23.8%)	40 (22.0%)	94411 (20.0%)
5 (Most deprived)	107 (24.6%)	521 (24.7%)	39 (21.4%)	94234 (20.0%)
Missing	7 (1.6%)	34 (1.6%)	0 (0.0%)	597 (0.1%)
Smoking status[§]: Never	135 (31.1%)	806 (38.3%)	65 (35.7%)	258073 (54.7%)
Previous	130 (30.0%)	578 (27.5%)	87 (47.8%)	160827 (34.1%)
Current	116 (26.7%)	428 (20.4%)	30 (16.5%)	50023 (10.6%)
Missing	53 (12.2%)	291 (13.8%)	0 (0.0%)	2746 (0.6%)
Comorbidities: GORD	<5 (<1.1%)	17 (0.8%)	6 (3.3%)	19596 (4.2%)
Cirrhosis			13 (7.1%)	466 (0.1%)
Hepatitis			16 (8.8%)	2367 (0.5%)
Liver diseases[‡]	34 (7.8%)	11 (0.5%)		
Diabetes	53 (12.2%)	89 (4.2%)	35 (19.2%)	23812 (5.0%)
Peptic ulcer	13 (3.0%)	24 (1.1%)	<5 (<2.7%)	5729 (1.2%)
Other drug use: Statins	112(25.8%)	572(27.2%)	45 (24.7%)	76505 (16.2%)
Aspirin	158 (36.4%)	659(31.3%)	43 (23.6%)	64755 (13.7%)
BMI: Normal\under weight			47 (25.8%)	154943 (32.8%)
Overweight			71 (39.0%)	199281 (42.3%)
Obese	102 (23.5%)	423 (20.1%)	64 (35.2%)	114531 (24.3%)
Missing\not obese	332 (76.5%)	1680 (79.9%)		
Missing			0 (0.0%)	2914 (0.6%)
Alcohol consumption[§]				
Never	91 (21.0%)	346 (16.4%)	30 (16.5%)	37871 (8.0%)
< 1 day per week			40 (22.0%)	106526 (22.6%)
1-2 days per week			34 (18.7%)	121501 (25.8%)
3-4 days per week			36 (19.8%)	108918 (23.1%)
>4 days per week			42 (23.1%)	95422 (20.2%)
Low	189 (43.5%)	1104 (52.5%)		
High	53 (12.2%)	93 (4.4%)		
Missing	101 (23.3%)	560 (26.7%)	0 (0.0%)	1431 (0.3%)

[†]Age at index date in Primary Care Clinical Informatics Unit data and age at baseline in UK Biobank data.

‡ Liver diseases includes cirrhosis, alcoholic and non-alcoholic fatty liver, and hepatitis.
§ Alcohol and smoking consumption based upon Read codes in Primary Care Clinical Informatics Unit data and questionnaire data in UK Biobank.

Table 2. The association between PPI and H2RA use and risk of liver cancer in Primary Care Clinical Informatics Unit.

	Cases n (%)	Controls n (%)	Unadjusted		Adjusted[†]		Fully adjusted[‡]	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
			n=2536		*n=2536*		*n= 1533*	
Any PPIs								
Never	289 (66.6%)	1618 (76.9%)	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Ever	145 (33.4%)	485 (23.1%)	1.74 (1.38,2.19)	<0.001	1.65 (1.28,2.12)	<0.001	1.80 (1.34,2.41)	<0.001
1-11 prescriptions	77 (17.7%)	259 (12.3%)	1.74 (1.30,2.32)	<0.001	1.69 (1.24,2.30)	0.001	1.92 (1.33,2.69)	<0.001
12+ prescriptions	68 (15.7%)	226 (10.8%)	1.73 (1.28,2.35)	<0.001	1.60 (1.15,2.23)	0.005	1.66 (1.13,2.45)	0.01
1-6 prescriptions	63 (14.5%)	214 (10.2%)	1.70 (1.25,2.33)	0.001	1.71 (1.22,2.38)	0.002	1.98 (1.35,2.89)	<0.001
7-12 prescriptions	16 (3.7%)	52 (2.5%)	1.83 (1.02,3.26)	0.041	1.61 (0.87,2.99)	0.13	1.58 (0.77,3.25)	0.213
13-36 prescriptions	49 (11.3%)	153 (7.3%)	1.81 (1.28,2.56)	0.001	1.65 (1.14,2.40)	0.008	1.68 (1.07,2.61)	0.022
37+ prescriptions	17 (3.9%)	66 (3.1%)	1.54 (0.87,2.72)	0.141	1.40 (0.75,2.60)	0.285	1.72 (0.87,3.38)	0.115
1-183 DDDs	59 (13.6%)	198 (9.4%)	1.74 (1.26,2.40)	0.001	1.77 (1.26,2.49)	0.001	2.06 (1.36,3.00)	<0.001
184-365 DDDs	16 (3.7%)	52 (2.5%)	1.76 (0.99,3.10)	0.053	1.53 (0.83,2.86)	0.178	1.70 (0.84,3.59)	0.145
366 - 1095 DDDs	38 (8.8%)	138 (6.6%)	1.60 (1.09,2.35)	0.017	1.46 (0.97,2.20)	0.072	1.34 (0.80,2.18)	0.245
1096 DDDs+	32 (7.4%)	97 (4.6%)	1.95 (1.26,3.01)	0.003	1.75 (1.09,2.82)	0.02	2.04 (1.23,3.66)	0.01
PPIs by type:								
Omeprazole (user v non-user)	93 (21.4%)	305 (14.5%)	1.68 (1.28,2.20)	<0.001	1.61 (1.20,2.16)	0.001	1.83 (1.30,2.56)	<0.001
Lansoprazole (user v non-user)	71 (16.4%)	256 (12.2%)	1.41 (1.05,1.89)	0.022	1.31 (0.96,1.80)	0.089	1.34 (0.93,1.93)	0.117
Any H2RAs								
Never	371 (85.5%)	1851 (88.1%)	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Ever	63 (14.5%)	252 (11.9%)	1.23 (0.91,1.66)	0.177	1.19 (0.87,1.64)	0.274	1.21 (0.84,1.76)	0.31
1-11 prescriptions	34 (7.8%)	161 (7.7%)	1.04 (0.70,1.54)	0.84	1.04 (0.69,1.57)	0.840	1.22 (0.75,1.96)	0.418
12+ prescriptions	29 (6.7%)	91 (4.3%)	1.56 (1.01,2.40)	0.044	1.45 (0.92,2.29)	0.113	1.22 (0.70,2.07)	0.496
1-6 prescriptions	27 (6.2%)	129 (6.1%)	1.03 (0.66,1.58)	0.907	1.06 (0.67,1.65)	0.830	1.25 (0.70,2.03)	0.406
7-12 prescriptions	7 (1.6%)	32 (1.5%)	1.10 (0.48,2.50)	0.821	1.00 (0.43,2.37)	0.988	1.10 (0.42,2.93)	0.845
13-36 prescriptions	20(4.6%)	61 (2.9%)	1.60 (0.95,2.68)	0.078	1.54 (0.90,2.65)	0.112	1.46 (0.79,2.72)	0.235
37+ prescriptions	9 (2.1%)	30 (1.4%)	1.49 (0.70,3.15)	0.295	1.24 (0.54,2.83)	0.604	0.75 (0.26,2.09)	0.580
1-183 DDDs	26 (6.0%)	124 (5.9%)	1.03 (0.66,1.60)	0.887	1.07 (0.68,1.70)	0.761	1.24 (0.73,2.12)	0.429
184-365 DDDs	8 (1.8%)	28 (1.3%)	1.39 (0.52,3.09)	0.415	1.19 (0.52,2.72)	0.682	1.47 (0.56,3.86)	0.437
366 - 1095 DDDs	20 (4.6%)	64 (3.0%)	1.52 (0.91,2.54)	0.111	1.50 (0.88,2.55)	0.137	1.33 (0.71,2.50)	0.374
1096 DDDs+	9 (2.1%)	36 (1.7%)	1.25 (0.60,2.62)	0.546	1.03 (0.46,2.30)	0.934	0.79 (0.30,2.07)	0.629
H2RAs by type:								
Cimetidine (user v non-user)	19 (4.4%)	92 (4.4%)	0.94 (0.56,1.57)	0.801	0.85 (0.49,1.47)	0.564	0.97 (0.50,1.88)	0.923
Ranitidine (user v non-user)	45 (10.4%)	166 (7.9%)	1.35 (0.95,1.90)	0.097	1.38 (0.96,1.99)	0.083	1.41 (0.91,2.15)	0.110

[†]Study matched on age, gender and general practice and model contains obesity, comorbidities in exposure period (including diabetes, coronary heart disease, myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, cerebrovascular accident, chronic obstructive pulmonary disease, mental illness, liver disease, peptic ulcer disease) and other medication use in exposure period (statins, aspirin)
[‡] Same model as [†] but alcohol and smoking added

Table 3. Sensitivity analysis for the association between PPI and H2RA use and risk of liver cancer in Primary Care Clinical Informatics Unit.

	Cases	Controls	Unadjusted		Adjusted[†]		Fully adjusted[‡]	
	n/N (%)	n/N (%)	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
PPIs (user versus non-user)								
Main analysis	145/434 (33.4%)	485/2103 (23.1%)	1.74 (1.38,2.19))	<0.001	1.65 (1.28,2.12)	<0.001	1.80 (1.34,2.41)	<0.001
Removing prescriptions 2 years before index	92/336 (27.4%)	320/1631 (19.6%)	1.59 (1.20,2.10)	0.001	1.50 (1.10,2.05)	0.010	1.65 (1.15,2.35)	0.006
Removing prescriptions 4 years before index	40/205 (19.5%)	149/988 (15.1%)	1.38 (0.92,2.06)	0.120	1.30 (0.83,2.02)	0.252	1.60 (0.97,2.64)	0.065
Lifestyle factors adjusted for using MI[§]	145/434 (33.4%)	485/2103 (23.1%)	1.74 (1.38,2.19)	<0.001	1.65 (1.28,2.12)	<0.001	1.67 (1.29,2.15)	<0.001
Ever use >= 3 prescriptions	104/434 (24.0%)	340/2103 (16.2%)	1.67 (1.29,2.16)	<0.001	1.57 (1.18,2.07)	0.002	1.61 (1.16,2.22)	0.004
Additionally adjusting for H2RAs[¶]	145/434 (33.4%)	485/2103 (23.1%)	1.74 (1.38,2.19))	<0.001	1.64 (1.27,2.12)	<0.001	1.79 (1.33,2.40)	<0.001
H2RAs (user versus non-user)								
Main analysis	63/434 (14.5%)	252/2103 (11.9%)	1.23 (0.91,1.66)	0.177	1.19 (0.87,1.64)	0.274	1.21 (0.84,1.76)	0.310
Removing prescriptions 2 years before index	51/336 (15.2%)	205/1631 (12.6%)	1.22 (0.88,1.70)	0.248	1.20 (0.84,1.71)	0.323	1.14 (0.75,1.74)	0.525
Removing prescriptions 4 years before index	29/205 (14.1%)	112/988 (11.3%)	1.24 (0.79,1.93)	0.352	1.20 (0.74,1.93)	0.464	1.03 (0.60,1.78)	0.907
Lifestyle factors adjusted for using MI[§]	63/434 (14.5%)	252/2103 (11.9%)	1.23 (0.91,1.66)	0.177	1.19 (0.87,1.64)	0.274	1.22 (0.89,1.69)	0.215
Ever use >= 3 prescriptions	48/434 (11.1%)	158/2103 (7.5%)	1.49 (1.05,2.10)	0.023	1.43 (1.00,2.06)	0.051	1.38 (0.90,2.12)	0.136
Additionally adjusting for PPIs[¶]	145/434 (33.4%)	485/2103 (23.1%)	1.74 (1.38,2.19))	<0.001	1.05 (0.76,1.46)	0.774	1.06 (0.72,1.55)	0.776

[†]Study matched on age, gender and general practice and model contains obesity, comorbidities in exposure period (including diabetes, coronary heart disease, myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, cerebrovascular accident, chronic obstructive pulmonary disease, mental illness, liver disease, peptic ulcer disease) and other medication use in exposure period (statins, aspirin)

[‡] Same model as [†] but alcohol and smoking added.

[§]Using multiple imputation to adjust for alcohol and smoking.

[¶]Model same as [†] and [‡] but additionally contains H2RAs and PPIs.

Table 4. The association between PPI and H2RA use and risk of liver cancer in UK Biobank.

	Users		Non-users		Unadjusted		Adjusted[†]	
	Cases	P-years	Cases	P-years	HR (95% CI)	P	HR (95% CI)	P
Any liver cancer					*cases=182*		*cases=182*	
Any PPIs	40	208846	142	1949660	2.08 (1.46, 2.96)	<0.001	1.99 (1.34, 2.94)	<0.001
Omeprazole	24	122894	158	2035613	2.01 (1.31, 3.09)	<0.001	1.78 (1.12, 2.83)	0.01
Lansoprazole	15	73849	167	2084658	2.01 (1.18, 3.42)	0.01	1.82 (1.05, 3.18)	0.03
Any H2RAs	8	39003	174	2119503	2.26 (1.11, 4.59)	0.02	1.70 (0.82, 3.53)	0.16
Ranitidine	8	36319	174	2122188	2.45 (1.21, 4.98)	0.01	1.82 (0.87, 3.79)	0.11
Hepatocellular carcinoma								
Any PPIs	20	208846	68	1949660	2.13 (1.29, 3.51)	<0.001	1.60 (0.91, 2.83)	0.11
Any H2RAs	5	39003	83	2119503	2.93 (1.19, 7.23)	0.02	1.24 (0.46, 3.37)	0.67
Intrahepatic bile duct carcinoma								
Any PPIs	17	208846	55	1949660	2.28 (1.32, 3.94)	<0.001	3.12 (1.72, 5.68)	<0.001
Any H2RAs	2	39003	70	2119503	1.41 (0.34, 5.73)	0.64	1.58 (0.38, 6.56)	0.53

[†]Model contains age at baseline, gender, deprivation, BMI, alcohol, smoking, comorbidities at baseline (including GORD, peptic ulcer disease, cirrhosis, hepatitis and diabetes) and other medication use at baseline (statins, aspirin).

Table 5. Sensitivity analysis for the association between PPI and H2RA use and risk of liver cancer in UK Biobank.

	Users		Non-users		Unadjusted		Adjusted[†]	
	Cases	P-years	Cases	P-years	HR (95% CI)	P	HR (95% CI)	P
Any liver cancer								
PPIs (main)	40	208846	142	1949660	2.08 (1.46, 2.96)	<0.001	1.99 (1.34, 2.94)	<0.001
PPIs (adjusting for H2RAs[‡])	40	208846	142	1949660	2.08 (1.46, 2.96)	<0.001	2.33 (1.58, 3.42)	<0.001
PPIs (2 year lag)	31	162986	120	1525719	1.89 (1.27, 2.81)	<0.001	1.79 (1.15, 2.77)	0.01
PPIs (4 year lag)	12	73143	65	689489	1.28 (0.69, 2.39)	0.43	1.30 (0.66, 2.55)	0.45
H2RAs (main)	8	39003	174	2119503	2.26 (1.11, 4.59)	0.02	1.70 (0.82, 3.53)	0.16
H2RAs (adjusting for PPIs[‡])	8	39003	174	2119503	2.26 (1.11, 4.59)	0.02	2.10 (1.03, 4.31)	0.04
H2RAs (2 year lag)	8	30557	143	1658149	2.73 (1.34, 5.57)	0.01	2.02 (0.96, 4.25)	0.06
H2RAs(4 year lag)	4	13984	73	748647	2.60 (0.95, 7.11)	0.06	2.26 (0.80, 6.39)	0.12
Hepatocellular carcinoma								
PPIs (main)	20	208846	68	1949660	2.13 (1.29, 3.51)	<0.001	1.60 (0.91, 2.83)	0.11
PPIs (adjusting for H2RAs[‡])	20	208846	68	1949660	2.13 (1.29, 3.51)	<0.001	2.06 (1.18, 3.58)	0.01
PPIs (2 year lag)	18	162986	59	1525719	2.19 (1.29, 3.73)	<0.001	1.62 (0.89, 2.94)	0.11
Any H2RAs (main)	5	39003	83	2119503	2.93 (1.19, 7.23)	0.02	1.24 (0.46, 3.37)	0.67
Any H2RAs (adjusting for PPIs[‡])	5	39003	83	2119503	2.93 (1.19, 7.23)	0.02	2.34 (0.94, 5.86)	0.07
Any H2RAs (2 year lag)	5	30557	72	1658149	3.36 (1.36, 8.32)	0.01	1.45 (0.53, 4.00)	0.47
Intrahepatic bile duct carcinoma								
PPIs (main)	17	208846	55	1949660	2.28 (1.32, 3.94)	<0.001	3.12 (1.72, 5.68)	<0.001
PPIs (adjusting for H2RAs[‡])	17	208846	55	1949660	2.28 (1.32, 3.94)	<0.001	3.11 (1.71, 5.66)	<0.001
PPIs (2 year lag)	11	162986	44	1525719	1.82 (0.94, 3.54)	0.08	2.63 (1.28, 5.40)	0.01
Any H2RAs (main)	2	39003	70	2119503	1.41 (0.34, 5.73)	0.64	1.58 (0.38, 6.56)	0.53
Any H2RAs (adjusting for PPIs[‡])	2	39003	70	2119503	1.41 (0.34, 5.73)	0.64	1.59 (0.39, 6.54)	0.52
Any H2RAs (2 year lag)	2	30557	53	1658149	1.85 (0.45, 7.58)	0.39	2.20 (0.52, 9.28)	0.28

[†]Model contains age at baseline, gender, deprivation, BMI, alcohol, smoking, comorbidities at baseline (including GORD, peptic ulcer disease, cirrhosis, hepatitis and diabetes) and other medication use at baseline (statins, aspirin).

[‡] Same model as [†] but additionally containing PPIs and H2RAs.

Statement of Interests

1. Authors' declaration of personal interests: All authors have no conflict of interest to declare.
2. Declaration of funding interests: This study was funded by Queen's University Belfast and the University of Aberdeen (providing funding to access PCCIU data), a CRUK Population Research Postdoctoral Fellowship for ÚCMcM (providing funding to access UK Biobank) and the Vietnam International Education Cooperation Department (providing funding for a PhD for KTT)

STROBE Checklist for study titled "Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies"

	Item No	Recommendation	Criteria addressed	Page	Section addressed
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**Yes**	**3**	**See Structured Summary.**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**Yes**	**3**	**See Structured Summary.**
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**Yes**	**5**	**See Introduction, paragraph 1 and 2.**
Objectives	3	State specific objectives, including any prespecified hypotheses	**Yes**	**5**	**See Introduction, paragraph 3.**
Methods					
Study design	4	Present key elements of study design early in the paper	**Yes**	**6,8**	**See Methods, Study design.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**Yes**	**6,7,8**	**See Methods, Study design.**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**Yes**	**6,8**	**See Methods, Study design.**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	**Yes**	**6**	**See Methods, Study design.**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**Yes**	**7,8**	**See Methods, Exposure and Covariates.**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment	**Yes**	**7,8**	**See Methods, Exposure and Covariates.**

		methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias	**Yes**	**9,10**	**See Methods, Statistical analysis – particularly the sensitivity analyses.**
Study size	10	Explain how the study size was arrived at	**N\A**		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**Yes**	**7**	**See Methods, Exposure data.**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**Yes**	**9,10**	**See Methods, Statistical analysis.**
		(*b*) Describe any methods used to examine subgroups and interactions	**Yes**	**9,10**	**See Methods, Statistical analysis.**
		(*c*) Explain how missing data were addressed	**Yes**		**See Methods, Statistical analysis, paragraph 3.**
		(*d*) If applicable, explain how loss to follow-up was addressed	**N\A**		
		(*e*) Describe any sensitivity analyses	**Yes**	**9,10**	**See Methods, Statistical analysis, paragraph 3 and 5.**
Results					
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**Yes**	**19**	**See Table 1.**
		(b) Give reasons for non-participation at each stage	**N\A**		
		(c) Consider use of a flow diagram	**N\A**		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Yes**	**19**	**See Table 1.**
		(b) Indicate number of participants with missing data for each variable of interest	**Yes**	**19**	**See Table 1, missing data clearly shown.**

		(c) Summarise follow-up time (eg, average and total amount)	**Yes**	**12**	**See Results, UK Biobank, paragraph 1.**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**Yes**	**21,24**	**See Table 2 and Table 4.**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**Yes**	**21,24**	**See Table 2 and Table 4.**
		(*b*) Report category boundaries when continuous variables were categorized	**Yes**	**21**	**See Table 2.**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**N\A.**		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**Yes**	**23,25**	**See Table 3 and Table 5 contains extensive sensitivity analyses.**
Discussion					
Key results	18	Summarise key results with reference to study objectives	**Yes**	**13**	**See Discussion, paragraph 1**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**Yes**	**13, 14**	**See Discussion, paragraph 3 and 4.**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**Yes**	**13,14,15**	**See Discussion.**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**Yes**	**15**	**See Discussion, paragraph 5.**
Other information					

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**Yes**	**26**	**See Statement of Interests.**