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## **Proton pump inhibitors and risk of all-cause and cause-specific mortality: a cohort study**

**Short title:** Proton pump inhibitors and mortality

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**What is already known about this subject:**

In non-interventional studies the prescription of proton pump inhibitors (PPI) has been associated with a large number of adverse health outcomes.

In a cohort of US veterans PPI prescription was associated with increased risk of all-cause and cause-specific mortality.

**What this study adds:**

Individuals prescribed PPIs seem to have poorer health than individuals prescribed alternative acid suppression therapy.

There was an association between PPI prescription and both all-cause (weighted hazard ratio 1.38, 95% CI 1.33-1.44) and cause-specific mortality, but analyses indicate that residual confounding is likely.

Confounding of non-interventional studies investigating PPIs is a major concern, in particular given the potential effect of these studies on patient and prescriber behaviour.

## **Abstract**

### **Aim**

To investigate the association between proton pump inhibitors (PPIs) and both all-cause and cause-specific mortality.

### **Methods**

We conducted a cohort study using the UK Clinical Practice Research Datalink GOLD database. We compared 733,885 new users of PPIs to 124,410 new users of H2 receptor antagonists [H2RAs]. In a secondary analysis we compared 689,602 PPI new users to 1,361,245 non-users of acid suppression therapy matched on age, sex, and calendar year. Hazard ratios for all-cause and cause-specific mortality were estimated using propensity score (PS) weighted Cox models.

### **Results**

PPI prescription was associated with increased risk of all-cause mortality, with hazard ratios decreasing considerably by increasing adjustment (unadjusted hazard ratio [HR] 1.65, 95% confidence interval [CI] 1.62-1.69; PS-weighted HR 1.38, 95% CI 1.33-1.44; high-dimensional PS-weighted HR 1.31, 95% CI 1.26-1.37). Short-term associations were observed with mortality from causes where a causal short-term association is unexpected (e.g. lung cancer mortality: PS-weighted HR at 6 months 1.77; 95% CI 1.39-2.25). Adjusted hazard ratios were substantially higher when comparing to non-users (PS-weighted HR all-cause mortality 1.96, 95% CI 1.94-1.99) rather than H2RA users.

### **Conclusions**

PPI prescription was strongly associated with all-cause and cause-specific mortality. However, the change in hazard ratios by (1) increasing adjustment and (2) between comparator groups indicate that residual confounding is likely to explain the association between poor health outcomes and PPI use, and fully accounting for this using observational data may not be possible.

**Keywords:** mortality, proton pump inhibitor, H2 receptor antagonist

Accepted Article

## Introduction

Proton pump inhibitors (PPIs) are a group of commonly prescribed drugs used to suppress gastric acid production. They are prescribed for a variety of indications including the treatment of dyspepsia, peptic ulcers, and gastro-oesophageal reflux disease, the eradication of *H. pylori*, and prophylaxis to prevent drug-induced gastrointestinal damage (e.g. from non-steroidal anti-inflammatory drugs [NSAID]).

Concern over the safety of PPIs has grown, given associations observed in non-interventional studies between PPI use and a range of outcomes including pneumonia, chronic kidney disease, cancer, and alcoholic liver disease [1-9]. Furthermore, recent non-interventional studies identified associations between PPI prescription and increased all-cause and cause-specific mortality [7, 10-12].

Previous safety concerns about PPIs have highlighted important limitations of statistical techniques used to account for differences between PPI users and non-users in non-interventional studies; several studies identified a harmful association between combined clopidogrel and PPI use, whilst randomised controlled trials (RCTs) found no clinically relevant interaction [13]. Given that PPIs are globally one of the most frequently used classes of drugs, it is vital that we are able to reliably evaluate their potential risks and benefits when making treatment decisions.

In this study we aimed to examine the association between PPIs and all-cause and cause-specific mortality, and to investigate the robustness of results to confounding by (1) applying different methods to adjust for confounding, (2) using different comparator groups, (3) examining the pattern of the associations across different time periods, 4) and including control outcomes not previously associated with PPI use.

## Methods

We conducted a cohort study comparing mortality among new users of PPIs to, in the first instance, new users of an alternative acid suppression drug, H2 receptor antagonists (H2RAs), and as a secondary analysis to non-users of either H2RAs or PPIs.

### Data source

The Clinical Practice Research Datalink (CPRD) GOLD database consists of primary care electronic medical records of people registered at one of over 700 general practices in the United Kingdom (UK). The dataset is widely validated for epidemiological research and broadly representative of the UK population in terms of age, sex and ethnicity [14]. Our study included the subset of CPRD GOLD practices that have consented to linkage with other datasets.

We incorporated linked data from the Office of National Statistics (ONS) death registration data, Hospital Episode Statistics Admitted Patient Care (HES APC) data, and Index of Multiple Deprivation (IMD) data. Date and cause of death were ascertained from ONS death registration data. In the UK all deaths are registered and cause of death is certified by a clinician. The number of hospital admissions in the 6 months prior to study entry, a covariate, was calculated from HES APC [15]. Socioeconomic deprivation, another covariate, was ascertained from postcode-based IMD data. The IMD is an index of relative socioeconomic deprivation based upon seven domains, which include income, employment, education and health [16].

### Study population

We included all adults in CPRD GOLD who were eligible for person-level linkage to HES APC and ONS, had acceptable research standard data, and who were prescribed a PPI or H2RA for the first time on or after the latest of: their 18<sup>th</sup> birthday, date of registration at current practice plus 1 year, first appointment with clinician after registration at current practice, date practice began contributing research quality data plus 1 year, or 02/01/1998 (start of ONS data coverage).

In a secondary analysis, to identify the extent to which confounding by indication may be an issue, we compared PPI users to matched non-users. We would expect similar results from both comparisons (PPI/H2RA and PPI/non-user) if our statistical models control for all confounding, and assuming no causal effect of H2RAs on mortality.

In calendar date order PPI users were matched to non-users of either acid-suppression medication (PPI or H2RA), who met the same date-based eligibility criteria as PPI users, on year of birth (+/- 2 years), sex, calendar year, and clinical practice. Up to two non-users meeting the matching criteria, and with the closest year of birth, were randomly matched (without replacement) to each PPI user. PPI and H2RA users were eligible as potential non-users prior to first PPI/H2RA prescription.

Cohort entry was defined as date of prescription for H2RA and PPI users, and for non-users as cohort entry date of matched PPI user. We followed individuals up until the earliest of death date, date the individual was no longer registered with the practice, date of last practice data collection, 17/04/2017 (end of coverage period of included ONS mortality data), date of first PPI prescription (H2RA users and non-users), or date of first H2RA prescription (non-users only).

## **Exposure**

Prescription of a PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole or esomeprazole) was the main exposure of interest. Choice of comparator group is an important consideration in observational studies of drug effects, with an active comparator generally considered the best approach to mitigate confounding. H2RA prescription (cimetidine, ranitidine, famotidine, nizatidine) was therefore chosen as the main comparator given that H2RAs are a gastric-acid suppressing medication used for similar indications to PPIs. PPIs are predated by H2RAs, but are now the most commonly prescribed acid-suppression therapy in the UK with superior efficacy observed for many indications in RCTs [17-20]. Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to Pharmacology 2019/20 [21, 22].

## Covariates

We adjusted for demographic and lifestyle variables, potential indications for PPI treatment, indicators of frailty, previous comorbidities and calendar year in our statistical models (Table 1 - further detail provided in additional file 1 - supplementary methods).

## Outcomes

All-cause mortality was the primary outcome. Cause of death was ascertained from the International Classification of Diseases (ICD) 9 or 10 code recorded for the underlying cause of death on the death certificate. Secondary outcomes included cause-specific mortality: 1) categorised into groupings used in the Global Burden of Diseases Study [23, 24]; 2) *a priori* causes that have previously been associated with PPIs; and 3) control outcomes we would not expect to be associated with PPIs.

Global Burden of Diseases Study groupings included the high-level categories of cause-specific mortality: communicable disease, non-communicable disease, and injury/external cause. Global Burden of Diseases groupings also included the lower-level categories: neoplasms; cardiovascular/circulatory; chronic respiratory diseases; liver cirrhosis; digestive other than cirrhosis; neurological; mental and behavioural; diabetes, urogenital, blood and endocrine; and musculoskeletal.

We included pre-specified individual causes of death where the cause was:

- Previously associated with PPIs and a short term causal association was considered plausible: pneumonia, acute kidney injury, *C. difficile* enterocolitis, atrial fibrillation/flutter, heart failure, and aortic aneurysm
- Previously associated with PPIs but where a short term causal association was considered to be unexpected based on disease pathogenesis: dementia and Alzheimer's, chronic kidney disease, hypertensive heart disease, ischaemic heart disease, lung cancer, mesothelioma, breast cancer, liver cancer, prostate cancer, gastric cancer, alcoholic liver disease, and chronic obstructive pulmonary disease (COPD)



We also included, as control outcomes, individual causes of mortality that had not been previously associated with PPIs: accidental trauma (excluding falls), and pulmonary embolism. We did not expect an association between PPI use and accidental trauma, which is unlikely to be confounded by underlying health status, whereas the association with pulmonary embolism may be affected by unmeasured differences between PPI exposed and unexposed individuals.

ICD codes for all outcomes are included in additional file 1 table S1.

### **Statistical analysis**

Propensity scores were used to adjust for differences in baseline covariates [25]. We generated propensity scores for PPI prescription using logistic regression, or conditional logistic regression (in the case of the matched non-user cohort[26]). In the PPI/non-user matched analysis the matching factors age, sex, and calendar year were excluded from the conditional logistic regression model. In the PPI/H2RA analysis propensity scores were estimated separately within each category of calendar year (1998-2003, 2004-2009, 2010-2015) given strong trends in prescribing of the two drugs over time.

A missing indicator approach was used for missing covariate information (for BMI, smoking status, and alcohol consumption). The missing indicator method has been found to be unbiased for propensity score analysis under assumptions that may be more plausible in the context of electronic health records than the complete records approach [27].

Estimated propensity scores were incorporated using average effect of treatment in the treated (ATT) weights. These weights estimate the average effect of treatment among individuals similar to the treated (PPI users) rather than in the overall study population [28]. ATT weights were chosen to increase comparability between the PPI versus H2RA, and PPI versus non-user analyses. By using ATT weights our effect estimates in both the PPI/H2RA and PPI/non-user comparisons pertain to the same population, PPI users.

ATT weighted Cox regression models, or ATT weighted stratified Cox regression models (in the case of the matched non-user cohort), were used to estimate the relative risk of each mortality outcome

with PPI exposure over 0 to 6 months (censoring follow-up at 6 months), 0 to 1 year, 0 to 10 years, and over all follow-up [29]. An early increase in risk for associations where a short-term association with outcome incidence is unexpected causally (based on disease pathogenesis) may indicate residual confounding.

As a secondary analysis, high-dimensional propensity scores (hd-PS) were used to investigate residual confounding of the primary analysis. The hd-PS approach selects a large number of covariates (500 in our study), prioritising for inclusion those with the greatest potential to confound the association of interest [30]. It has been suggested that the hd-PS may control for additional confounding by adjusting for proxies of unmeasured covariates (see additional file 1 - supplementary methods for further detail).

Sensitivity analyses included: 1) direct adjustment for covariates in the Cox model rather than propensity score weighting, 2) defining cause of death based on *any* listed cause rather than restricting to primary cause of death, 3) censoring follow-up at first PPI/H2RA treatment break (further detail in additional file 1 - supplementary methods), 4) censoring follow-up at first prescription of an H2RA among PPI users, 5) censoring follow-up on 31<sup>st</sup> December 2014 in order to only include follow-up when PPIs were solely available through pharmacy or prescription in the UK, rather than more generally in shops, 6) a post-hoc analysis excluding gastric cancer deaths from the definition of neoplasms deaths, and 7) propensity score trimming excluding individuals with propensity scores outside the range [0.1, 0.9] to assess sensitivity of findings to extreme weights [31-33]. Additionally, to quantify sensitivity to unmeasured confounding we calculated, using e-value formulae, the strength of association that an unmeasured confounder would need to have with exposure or outcome to fully explain the observed association [32].

All analyses were conducted using Stata MP Version 15.

## Results

The primary cohort consisted of 733,885 new users of PPIs and 124,410 new users of H2RAs (figure 1). PPI users were on average older, more often male, and had a higher baseline prevalence of comorbidities and co-medication use (table 2). Covariate balance improved after propensity score weighting with absolute standardised differences below 0.1 for all measured covariates.

### **Risk of mortality relative to H2RA users**

There were 95,489 (26.5 per 1,000 person-years [PY]) deaths observed among PPI users and 8,800 (16.1 per 1,000 PY) among H2RA users. Median follow-up was 4.1 years (interquartile range [IQR] 1.8-7.2) among PPI users and 3.0 years (IQR 0.8-7.0) years among H2RA users.

The risk of all-cause mortality was greater among PPI users relative to H2RA users (ATT weighted hazard ratio [wHR] 1.38; 95% confidence interval [CI] 1.33-1.44; figure 2). At the broadest level, cause-specific mortality was elevated from communicable (wHR 1.40; 95% CI 1.22-1.60), and non-communicable (wHR 1.39; 95% CI 1.34-1.45) diseases but not from injuries/external causes (wHR 1.00; 95% CI 0.78-1.26).

By more specific cause-of-death category, mortality was higher in PPI users compared to H2RA users from neoplasms (wHR 1.74; 95% CI 1.63-1.86), cardiovascular/circulatory causes (wHR 1.17; 1.10-1.25), chronic respiratory diseases (wHR 1.40; 95% CI 1.22-1.62), liver cirrhosis (wHR 1.95; 95% CI 1.10-3.46), digestive causes other than cirrhosis (wHR 1.43; 95% 1.20-1.69), and diabetes, urogenital, blood and endocrine causes (wHR 1.27; 1.06-1.51). Excluding gastric cancer deaths from neoplasms made little difference to the effect estimate for neoplasms mortality (wHR 1.72; 95% CI 1.61-1.83). There was no evidence of an increased risk of mortality from neurological, mental and behavioural, or musculoskeletal causes.

There was strong evidence of an association with mortality from a number of individual causes previously associated with PPI use including pneumonia, cardiovascular events, cancer, alcoholic liver disease, and chronic obstructive pulmonary disease. There was no evidence for an association

with the control outcome of mortality due to accidental trauma excluding falls (wHR 1.05; 95% CI 0.69-1.59), and the hazard ratio for the second control outcome, mortality from pulmonary embolism, was raised but had wide confidence intervals (wHR 1.33; 95% CI 0.85-2.09).

Adjustment via weighting reduced all hazard ratios (figures 2 and 3). For most outcomes, further adjustment using the hd-PS, reduced hazard ratios further towards the null (compared to a propensity score based on investigator chosen covariates).

### **Risk over different time periods**

Examining hazard ratios comparing PPI and H2RA users at different time points revealed that, for many of the outcomes, including outcomes (lung, liver and breast cancer) where a short-term causal association was unexpected, an association was apparent within 6 months of treatment initiation (figures 4 and 5, additional file 1 figure S1). For all-cause mortality the weighted hazard ratio was 1.34 (95% CI 1.25-1.43) over the first 6 months.

### **Non-user comparison**

For the secondary non-user comparison, 689,602 PPI users were matched (on age, sex, calendar year and clinical practice) to 1,361,245 non-users of acid suppression therapy (figure 1). No suitable match could be found for 44,283 (6%) of PPI users (characteristics of matched/non-matched patients in additional file 1 table S6). Matched non-users, relative to both PPI users and H2RA users, had a lower baseline prevalence of several comorbidities, and a lower mean number of GP appointments in the 6 months prior to cohort entry date (additional file 1 table S7).

### **Risk of mortality relative to non-users**

There were 86,825 (24.8 per 1,000 PY) deaths observed among matched PPI users and 69,402 (11.5 per 1,000 PY) deaths among non-users. Median follow-up was 4.3 (IQR 1.9-7.5) years among matched PPI users and 3.6 years (IQR 1.6-6.5) among non-users.

Weighted hazard ratios for all outcomes (with the exception of acute kidney injury, aortic aneurysm and COPD) were greater for PPI users compared to non-users, than for PPI users compared to H2RA

users (figures 2 and 3). For PPI use, relative to non-use, the weighted hazard ratio for all-cause mortality was 1.96 (95% CI 1.94-1.99) which was substantially higher than the comparison with H2RA users (wHR 1.38; 95% CI 1.33-1.44). Similarly, cause-specific mortality was substantially higher for a number of outcomes such as mortality from neoplasms (3.74, 95% CI 3.63-3.84 vs. 1.74, 95% CI 1.63-1.86), liver cirrhosis (4.10, 95% CI 3.36-5.01 vs. 1.95, 95% CI 1.10-3.46), and gastric cancer (14.59, 95% CI 11.16-19.08 vs. 2.35, 95% CI 1.39-3.99).

### **Sensitivity analysis**

To fully explain the lower bound of the observed association (HR 1.33) with all-cause mortality an unmeasured confounder would need to be associated with either exposure or outcome by at least RR 1.99 (risk ratio) and associated with both exposure and outcome by at least RR 1.33 [32].

Differences between estimates obtained from direct adjustment for covariates in the Cox model (adjusted HR all-cause mortality 1.39, 95% CI 1.35-1.42) relative to propensity score weighting (wHR 1.38, 95% CI 1.33-1.44) were minor (additional file 1 tables S8 and S9). Censoring follow-up among PPI users at first prescription of a H2RA similarly had minimal impact on effect estimates (wHR all-cause mortality 1.36, 95% CI 1.31-1.41; additional file 1 table S10). Censoring follow-up at treatment discontinuation consistently reduced effect estimates (wHR all-cause mortality 1.12, 95% CI 1.04-1.20; additional file 1 table 11) which may reflect both reduced follow-up and informative censoring whereby treatment is discontinued prior to death. Censoring follow-up at 31<sup>st</sup> December 2014 before PPIs became more widely available had little impact on effect estimates (wHR all-cause mortality 1.41, 95% CI 1.36-1.47; additional file 1 table S12). The differences between estimates of cause-specific mortality when defining cause of death based on any recorded, rather than primary recorded cause, were small (additional file 1 table S13). Propensity score trimming had minor effect on estimated associations (additional file 1 table S14 and S15).

## Discussion

In this cohort study we found associations between prescription of PPIs and both all-cause and cause-specific mortality. However, our findings also clearly indicated there are important differences between PPI users and comparator groups on characteristics predictive of death. PPI users were sicker and in order to draw any causal conclusions from these findings we must first decide whether these baseline differences were fully captured by measured covariates.

In line with previous non-interventional studies, at baseline PPI users had a higher prevalence of measures of comorbidity and indicators of frailty, both when compared to H2RA users and even more so when compared to non-users [10, 34]. We would therefore expect the PPI users to have a higher risk of mortality than either comparator group, which may bias a causal assessment of the observed association with PPIs.

With both comparator groups (H2RAs and non-users), hazard ratios decreased towards the null with increasing adjustment, indicative of increasing control of confounding. The unweighted hazard ratio for all-cause mortality was 1.65, which decreased to 1.38 after adjustment for covariates chosen by the study investigator, and to 1.31 after adjustment for the hd-PS (a methodology that has been suggested to control for additional confounding in studies using electronic health record data) [30].

However, it is not clear whether all confounding was fully controlled by any of these approaches. The hd-PS, as with any covariate adjustment method, requires confounders (or proxies of those confounders) to be measured to eliminate confounding.

Success in adjusting for confounding in all non-interventional studies hinges on the quality and completeness of data recording for all relevant variables. If we had accounted for all confounding, and the associations we reported were causal, we would expect the adjusted effect size to be very similar for both the non-user and H2RA comparator groups. However, the adjusted effect estimates were substantially higher when PPI users were compared to non-users, rather than H2RA users. This suggests residual confounding in one or both of these comparisons.

Our estimates are consistent with, though slightly higher than those observed in a cohort of United States veterans in a non-interventional study examining the association between PPIs and all-cause mortality [10]. In this previous cohort, the unadjusted and adjusted hazard ratios for all-cause mortality were 1.46 (95% CI 1.43-1.49) and 1.25 (95% CI 1.23-1.28), compared to 1.65, 95% CI 1.62-1.69 and 1.38 (1.33-1.44) in our study.

We did not find an association with the control outcome, mortality from accidental trauma excluding falls, which is expected given that this is less likely than other causes of death to be strongly related to health status. There was weak evidence for an association with the control outcome of mortality from pulmonary embolism, an outcome which might be affected by differences in underlying frailty between comparator groups, though confidence intervals were wide as this outcome was relatively rare in our cohort.

We found associations within six months of commencing PPI therapy for a number of very varied diseases that typically have a prolonged course from initial development to diagnosis (e.g. lung cancer). If causal, they would represent the actions of PPI on prevalent disease which could only be explained by a wide range of distinct biological mechanisms since the diseases themselves have different aetiologies and patterns of progression. Alternatively, such short-term associations could be explained by confounding, whereby PPIs are prescribed for symptoms in the early stages of a serious progressive illness. Notably, short-term associations are generally not reported in non-interventional studies of drugs as they are judged as unlikely to be causal, but we believe that reporting them is informative in showing a more rounded picture of the general problem of confounding.

Randomised controlled trials have not replicated the findings from non-interventional studies, providing further evidence that non-interventional studies are likely confounded. A recent randomised placebo-controlled trial of 17,598 patients with stable cardiovascular disease (median follow-up of 3.01 years) found no association between PPI use and all-cause mortality (HR 1.03, 95% CI 0.92–1.15), mortality from cardiovascular causes (HR 1.03, 0.89–1.20), or mortality from non-cardiovascular causes (1.02, 95% CI 0.87–1.21) [35]. Whilst it could be argued that any causal association may require a longer duration of exposure, these results at least mitigate against a short-to-

medium-term effect of PPIs on undiagnosed disease. No association was observed in the RCT with incidence of cause-specific mortality outcomes previously associated with PPI use in non-interventional studies including cancer, chronic kidney disease, dementia, pneumonia and COPD. The one exception to these negative findings was an increased incidence of enteric infections.

Previous non-interventional studies found differences in patient baseline characteristics similar to those observed in our study [10, 34, 36]. The range of comorbidities that are more prevalent among PPI users reflects the multiple indications for, and broad patient population prescribed, PPIs. No observational study can deal with unmeasured confounding, and in the case of prescribing of PPIs the data suggest that they are given at a greater rate to people who are frail, but we cannot fully assess how frail they may be. An unmeasured confounder associated with both exposure and outcome by a risk ratio of at least 1.33, and with either by at least 1.99, could potentially fully explain the observed association [32]. Given strong associations previously observed between frailty and mortality (RR > 2) and the possibility that more than one relevant variable may be under- or un-recorded, such unmeasured confounding is plausible [37]. This could be related to either the recording of presence or absence of a disease, but possibly more importantly, could also be related to the severity of a disease. For example, PPI users may have not only a higher prevalence of diseases such as hypertension and diabetes; they may also have more severe disease, which is less readily captured through routine health records.

Residual confounding may explain the wide ranging associations with PPI use observed both in the literature, where PPIs have been associated with over a dozen conditions, and in this study with cause-specific mortality from a number of causes [1-9, 38-40]. Notably, non-interventional research on the interaction between clopidogrel and PPIs similarly suffered from hard to account for confounding, and ultimately randomised trials suggested the harmful associations detected in many studies were not causal [41, 42].

Our study has several strengths. It is the largest study to date to examine the association of PPI prescription with all-cause and cause-specific mortality. Furthermore, our population was broadly representative of patients taking PPIs in the general population, given that the database used, CPRD



GOLD, is similar to the UK population on age, sex, and ethnicity [14]. The validity of health data recording in CPRD GOLD has been found to be very high [43].

There were limitations to our study. We expect some misclassification of acid-suppression drug usage as the data capture primary care prescriptions, but not over-the-counter or pharmacy medications sold without a prescription. However, sensitivity analysis limiting the study period to when PPIs were solely available through prescription or pharmacy (before January 2015), had little effect on results.

Given the large number of cause-specific mortality associations estimated, which increases the risk of observing some statistically significant associations that are purely due to chance, caution is warranted in the interpretation of any one individual association.

There will have been some misclassification due to non-adherence to prescribed medication, which is not recorded in these electronic health records. Assuming such misclassification was non-differential with respect to the outcome, this would tend to bias any causal association towards the null. There may be some misclassification of cause of death due to incorrect attribution of cause by the clinician certifying the death certificate. However, we expect misclassification to be non-differential with respect to PPI prescribing. Propensity score trimming did not lead to a systematic or major change in the hazard ratios, which we might have anticipated had it led to more valid estimates.

We have demonstrated that PPIs are associated with an increased risk of mortality from a wide range of illnesses. However, PPIs are preferentially given to people at increased risk of death. The change in hazard ratios with increasing adjustment and between comparison groups is indicative of residual confounding, and as such, we believe causality is unclear. Randomised trials are generally the ideal source of evidence to answer important questions about drug safety, but are not always available in sufficient size. Whilst non-interventional studies can often be helpful in assessing drug safety, we have presented an example where extra caution is needed in their design and reporting due to intractable confounding. We recommend a strong emphasis on informative sensitivity analyses, such as negative controls and quantitative bias analyses, to assess this problem in order to inform appropriate interpretation and application to clinical practice.

As with all medications, care should be taken to ensure PPIs are prescribed appropriately and for the correct duration. What is clear is that PPIs have a well-defined clinical benefit, and that uncertainty over their safety can lead to adverse unintended consequences [44].

Accepted Article

## **Acknowledgments**

This study evolved from an earlier project conceived and developed by our much missed colleague Adrian Root.

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## **Data availability:**

All data were obtained from the Clinical Practice Research Datalink (CPRD). CPRD data can be obtained by researchers following a successful application to CPRD.

This study is based in part on data from the CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. The study was approved by the Independent Scientific Advisory Committee (approval number: 17\_252). ONS/HES © (2020), re-used with the permission of The Health & Social Care Information Centre. All rights reserved

## **Contributors**

IJD, KM and LT conceived the study. All authors were involved in study design. JPB and JT conducted the data analyses. JPB wrote the initial draft. All authors interpreted the results, contributed to further drafts, and approved the final manuscript.

## **Ethics**

This study was approved by the London School of Hygiene and Tropical Medicine Research Ethics Committee (reference no. 15655) and by the CPRD Independent Scientific Advisory Committee (ISAC reference 17\_252).

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**Table 1: Covariates adjusted for in statistical models**

Demographic and lifestyle variables at baseline	Age, sex, index of multiple deprivation score (IMD), body mass index (BMI), smoking status, alcohol consumption
Potential indications for PPI treatment in 6 months prior to baseline:	Prescription for NSAID, aspirin, clopidogrel, oral anticoagulant or corticosteroid, upper gastrointestinal endoscopy, gastric cancer, gastro-oesophageal reflux disease, peptic ulcers, upper gastrointestinal (GI) bleeding, pancreatitis, cirrhosis, oesophagitis, Barrett's oesophagus, and <i>H. pylori</i> infection
Indicators of frailty in 6 months prior to baseline	Number of hospital admissions, number of general practitioner (GP) appointments, number of different drug types prescribed (based on distinct British National Formulary (BNF) chapters)
Ever recorded previous comorbidities	hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), cancer, non-viral liver disease, human immunodeficiency virus (HIV), chronic kidney disease (CKD), dementia, and diabetes mellitus
Other	Calendar year at cohort entry

**Table 2: Absolute standardised differences between PPI and H2RA users before and after weighting**

Characteristic*	Unweighted		Weighted		Unweighted ASD	Weighted ASD
	H2RA user	PPI user	H2RA user	PPI user		
Effective sample size	124,410	733,885	732,547.6	733,885		
Mean age in years	51.2	54.9	55	54.9	0.204	0.006
Mean BMI	26.5	27.2	27.2	27.2	0.118	<0.001
Calendar year						
1998-2003	56.7%	14.2%	14.2%	14.2%	1.135	0.001
2004-2009	31.3%	41.6%	41.6%	41.6%	0.210	<0.001
2010-2015	12.0%	44.2%	44.2%	44.2%	0.678	0.001
Female	57.3%	54.7%	54.1%	54.7%	0.052	0.014
Current smoker	24.3%	19.6%	19.7%	19.6%	0.119	0.002
Ex-smoker	24.3%	33.3%	33.2%	33.4%	0.195	0.005
High alcohol intake	2.7%	3.4%	3.4%	3.4%	0.039	<0.001
Below national median IMD	49.4%	51.8%	51.7%	51.8%	0.048	0.002
<b>In 6 months prior to PPI/H2RA treatment initiation</b>						
Mean no. of hospital admissions	0.3	0.4	0.4	0.4	0.052	0.001
Mean no. of GP appointments	4.8	5.9	6	5.9	0.165	0.003
Mean no. of BNF drug chapters	2.3	2.5	2.5	2.5	0.078	0.016
NSAID	21.3%	32.1%	31.5%	32.1%	0.236	0.012
Aspirin	11.7%	15.0%	14.9%	15.0%	0.093	0.004
Clopidogrel	1.6%	2.1%	2.2%	2.1%	0.036	0.009
Oral anticoagulant	2.0%	2.4%	2.5%	2.4%	0.022	0.01
Inhaled steroid	11.4%	12.8%	13.1%	12.8%	0.045	0.009
Systemic steroid	6.7%	7.2%	7.2%	7.2%	0.018	0.002
GORD	7.0%	8.4%	8.7%	8.4%	0.052	0.009
Oesophagitis	2.7%	3.5%	3.5%	3.5%	0.048	<0.001
<b>Ever previous</b>						
Hypertension	19.7%	26.1%	25.9%	26.1%	0.149	0.005
Coronary heart disease	8.0%	8.2%	8.3%	8.2%	0.01	<0.001
Peripheral artery disease	2.0%	2.2%	2.2%	2.2%	0.013	0.001
Cerebrovascular disease	3.7%	4.6%	4.8%	4.6%	0.043	0.011
COPD	2.6%	3.6%	3.7%	3.6%	0.055	0.003
Cancer	7.4%	10.1%	10.5%	10.1%	0.093	0.012
CKD	8.8%	13.9%	13.9%	13.9%	0.15	0.002
Diabetes	5.2%	7.7%	7.7%	7.7%	0.097	<0.001

\* Only covariates with a frequency greater than 2% among PPI users or H2RA users are included in this table. Standardised differences for all measured covariates including those occurring with frequency less than 2% are provided in additional file 1 table S2.

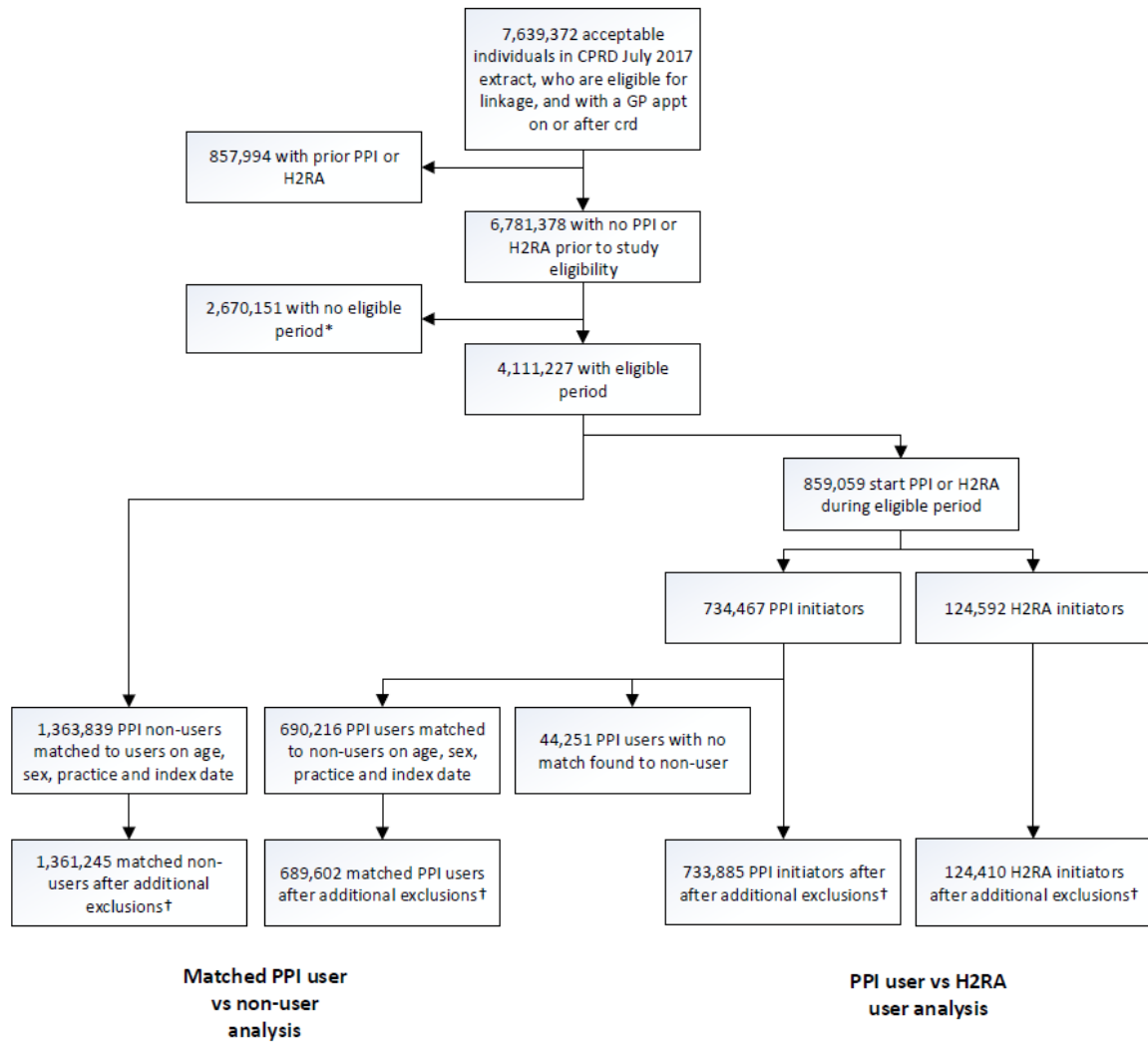
Abbreviations: ASD, absolute standardised difference; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor; BMI, body mass index; IMD, Index of Multiple Deprivation; GP, General Practitioner; BNF, British National Formulary; GI, gastrointestinal; GORD, gastro-oesophageal reflux disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

\* Beginning of eligibility is latest of on one year after current registration date, one year after up-to-standard date, study start (02/01/1998), 18<sup>th</sup> birthday, and first GP appointment after current registration date. End of eligibility is earliest of transfer out date, last collection date, study end date (31/12/2015) and death date.

† Additional exclusions occurred to remove individuals with missing Index of Multiple Deprivation data, and when ONS death date obtained.

Abbreviations: CPRD, Clinical Practice Research Datalink; GP, general practitioner; crd, current registration date i.e. date of registration at current practice; PPI, proton pump inhibitor; H2RA, H2 receptor antagonist

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**Figure 1: Study flow chart**

Hazard ratios and 95% CI are plotted here and listed in additional file 1 tables S3 and S4. Abbreviations: PPI, proton pump inhibitor; PS, propensity score; H2RA, H2 receptor antagonist; hd-PS, high-dimensional propensity score.

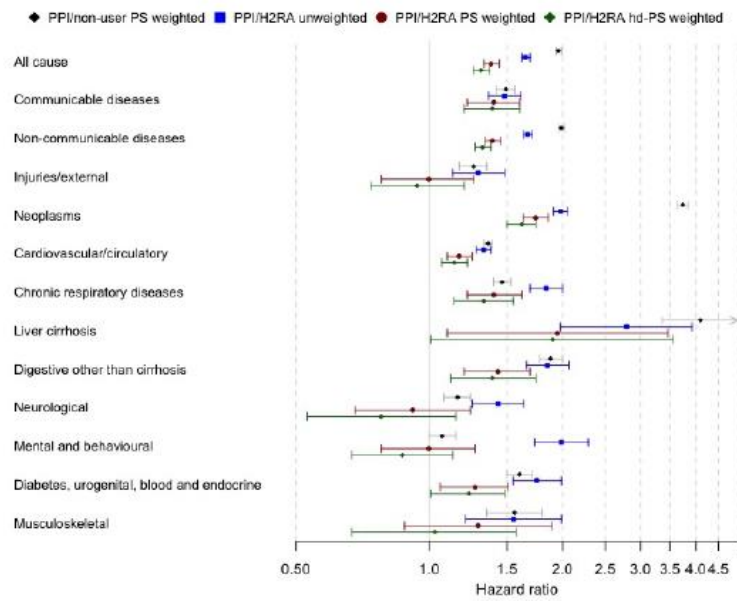


Figure 2: Forest plot of the associations between PPI prescription and both all-cause and broad-level cause-specific mortality

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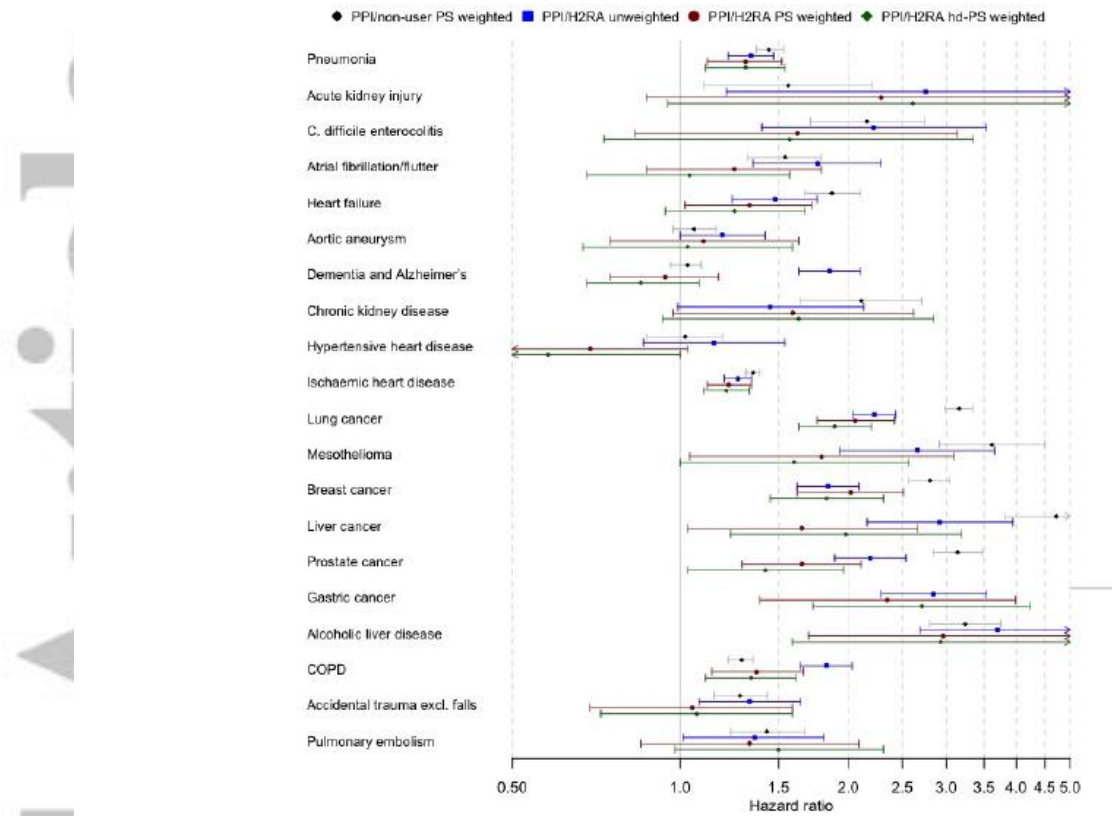


Figure 3: Forest plot of the associations between PPI prescription and mortality from individual specified causes

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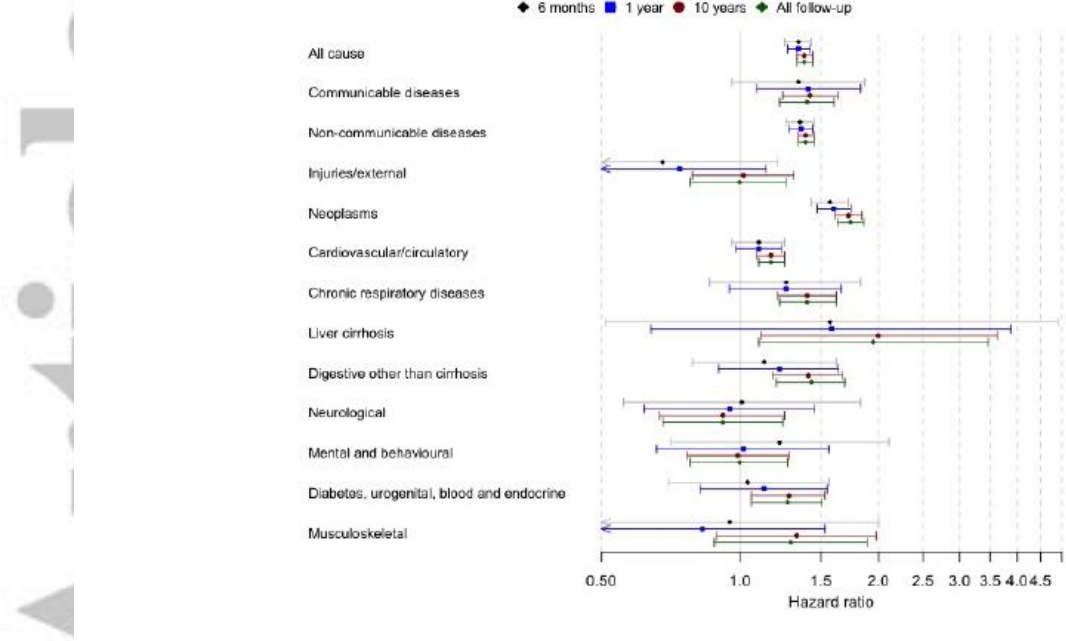


Figure 4: Forest plot of the associations between PPI prescription, relative to H2RA prescription, and both all-cause and broad-level cause-specific mortality over up to 6 months, 1 year, 10 years, and all follow-up

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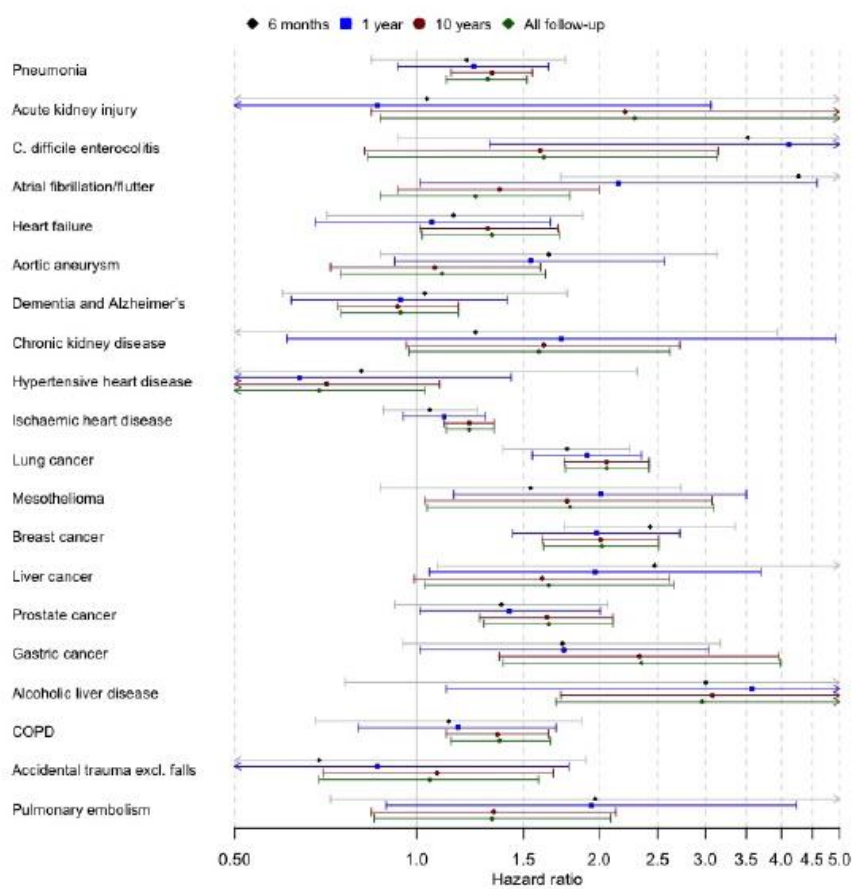


Figure 5: Forest plot of the associations between PPI prescription, relative to H2RA prescription, and mortality from individual specified causes over up to 6 months, 1 year, 10 years, and all follow-up