EPIDEMIOLOGY OF PROTON PUMP INHIBITORS THERAPY: AN EXAMINATION OF THE USE AND SAFETY IN GENERAL PRACTICE

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Thesis submitted to The University of Nottingham for the degree of Doctor of Philosophy

April 2017

Abstract

Background:

Proton pump inhibitors (PPIs) have become the cornerstone of medical treatment for acid-related gastrointestinal disorders. To date, there is a distinct lack of understanding about the recent UK trends in PPI use and evidence about the association between the increased risk of these drugs and the potential adverse effects, in particular the risk of infection, remains questionable. The publication of contradictory findings in several research studies further compounds this situation.

Aim and Objectives:

This thesis aimed to examine the epidemiology of PPI use in general practices in the UK, and the side effects of PPI, mainly their proposed infective complications.

The specific objectives were:

• To determine the prevalence and pattern of PPI prescription, and to identify the practices employed to reduce PPI use in the UK general population.

• To examine the risk of community-acquired pneumonia before and after the administration of PPI and to assess whether unmeasured confounding explains this association.

• To determine whether the mechanism by which PPIs induce an increased risk of infection is supported by the same mechanism acting in another cause of achlorhydria, pernicious anaemia.

Methods:

This thesis describes work conducted using the UK's Clinical Practice Research Database (CPRD) and, for some studies in this project, a subset of the CPRD linked to the hospital records from the Hospital Episodes Statistics (HES) database. Firstly, the CPRD was used to estimate the annual prevalence of PPI use during the period 1990-2013. In this study, new users of PPI therapy who had five years of follow-up data were identified to describe patterns of cessation and duration of PPI use. Secondly, cohort (analysed using Cox regression and prior event rate ratio) and self-controlled case series studies were conducted to examine the risk of community-acquired pneumonia and PPI exposure. Thirdly, a cohort of pernicious anaemia patients was used to estimate the risk of infections (community-acquired pneumonia and Clostridium difficile infection) compared to controls to examine whether a reduction in gastric acidity might be the underlying mechanism of the increased risk of these infections.

Findings:

1) There was a considerable increase in the administration of PPI prescriptions in UK general practice such that both the period and point prevalence of PPI use increased between 1990 and 2012 (period prevalence increased from 0.2% to 14.8% and point prevalence from 0.03 % to 7.7%). Of new users of PPI therapy, 27% used PPI therapy over a long-term basis (≥1 year continuously), while 4% remained on PPI therapy for five years. Clear attempts to step down the dosage were identified in 41% of long-term users.

2) Among 320, 000 patients, including 160 ,000 new PPI users, the risk of community-acquired pneumonia was 1.67 (95% confidence interval (95%CI) 1.55 to 1.79) times higher for patients exposed to PPIs than it was for the controls. Among the 48,451 PPI-exposed patients with a record of community-acquired pneumonia, the relative incidence rate ratio was 1.19 (95%CI 1.14 to 1.25) in the 30 days after a PPI prescription but was higher in the 30 days before a PPI prescription (1.92, 95%CI 1.84 to 2.00). This reduction in the increased risk in PPI users after prescription was also reflected in the prior event rate of 0.91 (95%CI 0.83 to 0.99).

3) A total of 45,467 pernicious anaemia patients were identified and matched to 449,635 controls. Patients with a

pernicious anaemia diagnosis had a higher risk of developing community-acquired pneumonia than the control group (adjusted hazard ratio(HR)1.24, 95%CI 1.21 to 1.26); however, this risk decreased when a stricter definition of pernicious anaemia was applied, and the data was further restricted to incident diagnosis. The findings also suggest that pernicious anaemia patients have a 57% increased risk of Clostridium difficile infection (adjusted HR 1.57, 95% CI 1.40 - 1.76) and this association persisted when we limited the analysis to a subgroup with a more restrictive definition of pernicious anaemia diagnosis, or to incident cases.

Conclusions:

This research revealed that there was a high prevalence of PPI prescribing in the primary care setting and that there are considerable opportunities available to reduce the cost and side effects of PPI use through improving adherence to recommended withdrawal strategies. In addition, the studies investigating the proposed infective complications of PPI use on which we focussed in this thesis add important data to the development of a safety profile of PPI use.

Acknowledgments

I would like to express my sincere thanks to my supervisors, Dr Timothy R Card and Dr Colin J Crooks, for introducing me to the original topic and the guidance and constructive advice they have provided throughout this work. The initial idea for this PhD was suggested my principle supervisor, Dr Tim Card, and I continued to develop the project under the guidance of my supervisors. I have learnt so much from them, and their feedback and support have been invaluable.

I would also like to thank King Saud bin Abdulaziz University for Health sciences- Saudi Arabia , represented by the Saudi Cultural Bureau-London funding my PhD studies at the University of Nottingham.

I express my since thanks to my PhD colleagues within the Division of Epidemiology and Public Health for their advice on Stata and their moral support.

Finally, a special thanks to my lovely husband, who has given me his total support throughout the highs and lows of this PhD, and to my parents for their care.

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List of Abbreviations

BNF	British National Formulary
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
FDA	Food and Drug Administration
GORD	Gastroesophageal Reflux Disease
GP	General Practitioner
HES	Hospital Episode Statistics
HR	Hazard Ratio
H2RA	H2-receptor antagonist
ICD	International system for classification of diseases
IMD	Index of Multiple Deprivation
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
ONS	Office for National Statistics
OR	Odd Ratio
OTC	Over-the-counter
PERR	Prior Event Rate Ratio
PPI	Proton pump inhibitor
SD	Standard deviation
UK	United Kingdom
(H+/K+ ATPase)	Hydrogen Potassium ATPase

Chapter One

Background and Rational For the Thesis

1.1. Introduction

Proton pump inhibitors (PPIs) have become the cornerstone of medical treatment for acid-related gastrointestinal disorders. Since their introduction, they have been widely adopted in many clinical settings because of their efficacy and good safety profile. As PPIs have become more widely used in primary and secondary care settings, a number of concerns have been raised about their potential side effects. However, the legitimacy of these concerns remains uncertain. Therefore, building upon the knowledge and information contained within existing literature, this thesis aims to achieve the following:

- To examine the patterns of PPI use and the practices employed to reduce PPI use in the general practices in the UK.
- To investigate the effect of the confounders on one of the suspected health concerns associated with PPI, community-acquired pneumonia.
- To bridge the gap in understanding of the possible mechanism by which PPI patients exhibit an increased susceptibility to infection by examining the risk of infection (community-acquired pneumonia and Clostridium difficile infection) in patients with

pernicious anaemia who have a similar low stomach acidity to patients prescribed PPIs.

This section provides a brief overview of acid-peptic disease, the role of PPI, and the current evidence on some of the potential side effects of PPI use. This chapter also contains an outline of each of the subsequent chapters, which includes a description of the studies carried out for this thesis.

1.2. Overview of Acid-Peptic Diseases

Gastric acid secretion is essential to the functionality of the stomach, and both neural and hormonal control stimulate acid secretion(1). Acid is generated through a complex series of reactions controlled by at least three types of receptors (histamine, gastrin and acetylcholine) that regulate the translocation and activation of the hydrogen potassium ATPase(H^+/K^+ ATPase) enzyme (the proton pump enzyme), in the plasma membrane of parietal cells(2,3). The enzyme secretes acid by exchanging cytoplasmic Hydrogen(H^+) ions with extracellular Potassium(K^+) ions and later these H^+ ions couple with chloride (Cl^-) ions to form the gastric acid(2,3). The pH of the gastric acid is very low, pH1.5 to 3.5 in the stomach lumen(4). Acid secretion in the

stomach exhibits a circadian rhythm. During the day there is an increase in acid secretion followed by a gradual decrease in the night(5). Any pathology that causes an imbalance between the rate of secretion of gastric acid and the degree of protection afforded by mucosal barrier may result in acid-peptic disorders.

Acid-related disease is a term that is used to describe a variety of conditions that cause symptoms related to the upper gastrointestinal tract. It includes both organic diseases, in which pathological changes can be identified and taken as proof of the condition, like gastroesophageal reflux disease (GORD) and peptic ulcer disease, and functional disorders, where no obvious cause is identified (functional dyspepsia)(6). The term "dyspepsia", which refers to a complex of symptoms that arise from the upper gastrointestinal tract and are present for four weeks or more(7), is commonly used to describe symptom profiles in acid-related diseases. Other symptoms include heartburn, abdominal pain or discomfort, fullness, nausea, bloating, and dysphagia.

GORD refers to pathological reflux of gastric contents into the oesophagus leading to troublesome symptoms and/or complications(8,9). It represents a spectrum of clinical manifestations ranging from reflux without significant symptomatic manifestation or oesophageal mucosal damage, to more severe pathological impact and complications including peptic stricture, erosive oesophagitis, and Barrett's oesophagus(8). In some cases, patients may develop a malignant condition such as adenocarcinoma(10). Heartburn is a major feature of GORD. Other typical symptoms include regurgitation, epigastric pain and dysphagia. On the other hand, peptic ulcers (gastric or duodenal) are defects in the superficial epithelial mucosa that penetrate down into the muscularis mucosa(1,11,12). Peptic ulcer disease is a common clinical problem and it occurs mainly in the stomach or proximal duodenum. The most important risk factors are infection with Helicobacter pylori (H. pylori) infection, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) use. Rare causes include the unopposed hypergastrinemia of Zollinger-Ellison syndrome(8). Epigastric pain is the most common presenting symptom of peptic ulcer disease, and this has a variable relationship with food.

1.3. Prevalence of Acid-Peptic Disorders

It is common for patients to present with acid-peptic disorders in daily general practice and these account for about 3% to 10% of all consultations in primary care(6,13–15). Previous studies have reported a high prevalence of upper gastrointestinal tract symptoms, with between 28% and 40% of the general population being affected(16–18). GORD stands out as one of the most common acid-peptic disorders(19–22). Epidemiological data have reported an increasing prevalence of GORD, and it is estimated that up to 20% of the population in Western countries have symptoms of heartburn and/or regurgitation at least weekly, and while the reported prevalence of GORD in Eastern countries is less than 5%; this rate appears to be increasing(19,20).

Peptic ulcer disease also remains a common disorder. It is more prevalent in developing countries and is related to high rates of H. pylori infection. As the prevalence of peptic ulcer disease declined in the developed countries because of the eradication of H. pylori infection, the increase in use of NSAIDs led to an increase in the occurrence of NSAID-induced gastric ulcers(11,12).

Individuals with peptic ulcer disease are at risk of developing complications, such as haemorrhage, perforation, and gastric outlet obstruction, and the mortality among patients with these complications is high(12,23).

These conditions, therefore, represent a substantial burden in terms of quality of life and health care expenditure due to their prevalence as well as their chronicity and recurrent natural history (13,20,24–26). Patients with more severe and persistent GORD are likely to have reduced work productivity as well as utilising healthcare services more frequently (13,26). Hence, appropriate management is essential to minimise healthcare expenses and improve the quality of life of the patients affected.

1.4. PPI use in Medical Management of Acid-Related Diseases

The therapeutic goals for patients with acid-related disorders are to obtain rapid and complete symptom relief. These goals may be achieved by both medical, and in many cases surgical, treatment modalities(3). The key objective of the medical treatment of acid-related disease is to increase the intragastric pH by

potent and safe drugs that relieve symptoms and prevent complications. The principal pharmacological methods to achieve this are using histamine (H2)-receptor antagonists (H2RAs) to block H2-receptors and PPIs to stop acid production at its source.

H2RAs inhibit gastric acid secretion by reversibly competing with histamine to bind to H2-receptors on the parietal cells(27,28). H2RAs were for a period the mainstay of therapy of acid-related disorders and demonstrate reasonable efficacy in decreasing basal acid production(29). However, H2RAs are partially effective and evidence from clinical practice and clinical trials has shown that H2RAs achieve suboptimal acid suppression and patients develop tolerance with prolonged therapy, which limits the extent to which these drugs are effective at managing acid-related disorders, especially GORD(27–30).

1.4.1. Mechanism of action of PPIs

The introduction of PPIs in 1980 has challenged the primacy of H2RAs due to the fact that they demonstrate a more effective acid-suppressing ability than H2RA(29). There are currently five PPIs available in the UK:

omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole(BNF, Section 1.3.5(31)). All PPIs have broadly similar mechanisms of action, despite some variations in their potential pharmacokinetics and drug interactions(32,33).

PPIs are weak bases, and their activation occurs in an acid environment at the secretory canalicular surface of the parietal cell in the stomach(34). They block the final pathway of production of acid by irreversibly inhibiting the activity of the gastric proton pump, H^+/K^+-ATPase enzyme in the parietal cell (34,35). They permanently inactivate those protein pumps and the only way to start producing acid again is by regenerating these proton pumps. The inhibition of this enzyme and gastric acid secretion occurs rapidly after the first dose of PPI. Only 70% of proton pump enzymes are inhibited after the first oral dose, and it takes up to five days for the PPIs to reach their optimal efficacy of inhibition of acid secretion(34,35).

Comparative studies of the five recognised PPIs have shown little overall difference between them in terms of their ability to manage acid-related disorders when used

in their standard dose(29,32,36). The majority of patients respond well to a once-daily dose, which provides effective healing and symptom relief; however, some patients, in particular, those with severe and complicated disease, need more aggressive therapy. Studies have reported that PPIs are more effective at controlling GORD symptoms and demonstrate higher healing rates than H2RA(37,38). Research has found that 60% of GORD patients treated with H2RA achieved symptomatic relief, whereas this figure was 83% in patients treated with PPIs, indicating that PPIs are more effective than H2RAs for the empirical treatment of GORD(38). PPIs are also part of the eradication treatment of H. pylori infection, which has dramatically revolutionised the approach to the treatment of peptic ulcer diseases and curing rates(11,12). For non-Helicobacter pylori peptic ulcers H2RAs alone are effective, but PPIs are now the preferred agents because of their ease of use and superior efficacy especially to heal ulcers that are resistant to high dose H2RA(3). In addition, PPIs are superior to H2RAs in preventing clinically important and overt gastrointestinal bleeding(39).

1.4.2. Approved indications of PPIs

Several clinical trials have verified the clinical effectiveness of PPI use in the management of acid-related disease and the efficacy of these drugs was reflected in prescribing guidelines and practices. In the UK, the National Institute for Health and Care Excellence (NICE) guidelines suggest PPIs as first-line therapies for the treatment of many conditions, including uninvestigated dyspepsia, GORD, H. pylori eradication therapy, and gastric and duodenal ulcers(Table 1-1)(7). The average course of treatment for these conditions is between 4 and 8 weeks. The long-term prescription of PPIs is indicated in patients with erosive oesophagitis or complications of gastro-oesophageal diseases, such as oesophageal strictures, and to reduce the degradation of pancreatic enzyme supplements(7,31). Patients who require long-term treatment with a NSAID may be co-prescribed a PPI for ulcer prophylaxis.

Table 1-1 Categories of potential indications for proton pump inhibitor prescription with the proposed management for each indication listed

Potential indication category	Description	Recommended management
Dyspepsia	Dyspepsia in addition to other symptoms (epigastric pain, indigestion, stomach upset)	Offer empirical full-dose PPI therapy for 4 weeks to people with dyspepsia
Uncomplicated GORD	Heartburn, esophagitis	Full dose PPI for 4 or 8 weeks If symptom recur after initial treatment, the lowest dose of PPI should be offered to control symptoms For severe oesophagitis, full dose of PPI for 8 weeks. If treatment fails, consider switching to another full dose PPI or high dose of the initial PPI.
Complicated GORD	Barretts oesophagus, oesophageal strictures and stenosis, ulcer of oesophagus	Remain on long-term full-dose PPI therapy
Peptic ulcer below oesophagus	Including complicated and un complicated gastric and duodenal ulcer(acute/chronic)	Full-dose PPI for 4 to 8 weeks to people who have tested negative for H pylori who are not taking NSAIDs. If symptoms recur after initial treatment, the lowest dose of PPI have to be offered to control symptoms.

NSAID prophylaxis	Non-steroidal anti-inflammatory drug induced gastric ulcer Anti-platelet induced gastric ulcer	In patients who need to continue NSAID treatment after an ulcer has healed, the dose of proton pump inhibitor should normally not be reduced because asymptomatic ulcer deterioration may occur.
Helicobacter therapy	Helicobacter gastritis, Helicobacter breath test positive	In combination with antibiotics for H pylori eradication course
Reduction of pancreatic enzyme degradation	Cystic fibrosis and chronic pancreatitis	A proton pump inhibitor can be used to reduce the degradation of pancreatic enzyme supplements in patients with cystic fibrosis (Based on BNF, Section 1.3.5(31)).
Gastritis & duodenitis	Acute or chronic gastritis/duodenitis without mention of ulcer, gastric erosion	An initial two week course of PPIs as a healing dose, to see if the condition is acid-related.

GORD= Gastro-oesophageal reflux disease; NSAID nonsteroidal anti-inflammatory drug
* The recommended management for each indication is based on the NICE guideline recommendation unless otherwise stated(7).

1.4.3. Utilisation of PPI

The amount of PPIs prescribed has increased significantly over the past few decades. Reports from UK, America, Australia, and many European countries have documented increased use in many clinical settings with subsequent cost implications(40–47). According to the Prescription Cost Analysis report, in the UK in the year 2000, around 11,126,000 prescriptions for PPIs were dispensed(48) and this increased to 43,127,000 in 2011(49). Since 2006, health authorities have encouraged clinicians to prescribe the low-cost generic PPIs that are available with the intent of achieving financial savings without affecting clinical outcomes. Although these efforts led to a reduction in expenditure on PPIs in the UK, it did not decrease the rate at which PPIs were prescribed, and the cumulative administration of PPI prescriptions subsequently led to an increase in healthcare costs(50). Thus, in 2010, PPIs became one of the top 20 drugs with the greatest net ingredient cost in the UK(51).

Although a few studies have described the pattern of PPI use in the UK (47,52–54), further information on the normal usage patterns of PPI treatment and the proportion of patients who receive PPI therapy over a long duration in the UK would be useful to improve understanding of PPI utilisation in general

practices. This may have important implications for any evaluation of the appropriateness of PPI utilisation and the health economics aspects of PPI treatment.

1.5. Safety Concerns Regarding PPI Use

The effectiveness of PPIs has led to the overutilization of these drugs in different health settings, thereby exposing patients to potential risks(42,45). These potential consequences have ranged from malabsorption of vitamins and minerals, drug interaction, through to an increased risk of infection and fracture. In addition, more recent reports have linked PPI use to cardiac infarction, dementia, and renal complication(55–61).

The following section will examine the previously published literature on the potential adverse effects of PPI use with a specific focus on the effects on absorption of vitamin B12 and minerals, and the susceptibility to infection (community-acquired pneumonia and enteric infection).

1.5.1. Effects on absorption of vitamin B12, calcium, and magnesium.

PPIs can alter the bioavailability and absorption of key vitamins and minerals in both the stomach and small intestine as described in the following sections.

1.5.1.1. VitaminB12

Gastric acid is needed for dietary vitamin B12 to dissociate from the protein, allowing its absorption in the terminal ileum after it is combined with the intrinsic factor(62,63). A case-control study reported that the chronic use of acid suppression medication was associated with an increased risk of vitamin B12 deficiency (odds ratio [OR] 4.45, 95% confidence interval [CI] 1.47-13.34)(64). While many recent studies suggest an increased risk of vitamin B12 deficiency with chronic PPI use, especially in older members of the population(65,66), most current evidence is based on case reports and small and non-randomised studies. At present, this association remains controversial and is still not confirmed; therefore, there is no evidence to suggest there is a requirement for additional supplementation or for monitoring the serum cobalamin levels in patients who undergo long-term PPI therapy.

1.5.1.2. Calcium

The effect of PPIs on calcium absorption, metabolism, and bone fracture has been more controversial than its possible

effect on vitamin B12 status. Many studies have examined the association between PPI and the risk of fracture to determine whether the effect of PPI on calcium metabolism could result in clinically significant alterations in fracture risk(67–71). The majority of these studies reported an increase in fractures with PPI use. In a meta-analysis of these observational studies, individuals taking PPIs have a 30% increase in the risk of hip fracture (95% CI 1.31 to 1.85) and 50% increase in the vertebra fracture (OR 1.14 to 1.37)(71,72). In light of this evidence, in 2011, the Food and Drug Administration (FDA) published an advisory communicating the fact that patients who are exposed to a prolonged and high doses of PPI may be at an increased risk of fracture(73).

Nevertheless, the potential mechanisms behind this increased risk have not yet been proven. Theoretically, an acidic medium is essential to release ionised calcium from insoluble calcium salts so that it can be absorbed in the upper small intestine(63). However, this supposition was examined in trials that examined short-term gastric acid suppression by PPIs and found that these drugs did not disrupt intestinal calcium absorption in healthy young adults(74). On the other hand, Merriman et al. reported an increase in hip fracture risk in patients with pernicious anaemia who have no acid production

(achlorhydria) compared with the controls(75). This suggested that PPI-associated hypochlorhydria could play an important role in calcium absorption. Other postulated mechanisms through which PPI use is linked to an increased fracture risk include the inhibition of osteoclast-mediated bone resorption, and a reduction in the absorption of vitamin B12 that disturbs collagen cross-linking and is associated with hip fracture risk(63).

1.5.1.3. Magnesium

In recent years, studies have linked PPI use with a rare and serious electrolyte imbalance: hypomagnesemia, a disturbance in which the blood magnesium level is abnormally low. This was first described in 2006 by Epstein et al. (76) who examined two cases of severe hypomagnesemia and hypocalcemia associated with the use of PPI, in which the level of magnesium normalised after PPI discontinuation. Since then, many other case reports(77) and observational studies, that were either small or hospital-based, have reported an association between the chronic use of PPI and hypomagnesemia (Table 1-2). In 2001, the Medicines and Healthcare products Regulatory Agency (MHRA)(78) and the FDA (79) warned of the risk of hypomagnesaemia following long-term PPI use and GPs are now advised to consider

checking a baseline serum magnesium level in patients who are about to commence PPI therapy.

Indeed, there is no accepted pathophysiological mechanism of this association. Magnesium homeostasis depends on the balance between intestinal absorption and renal excretion. Reports have suggested PPIs can cause renal mediated hypomagnesemia and these are supported by evidence that PPI induces acute interstitial nephritis; however, reports that link PPIs to hypomagnesemia have consistently demonstrated normal renal magnesium conservation(80). The alternative, and accepted, mechanism for PPI-induced hypomagnesemia, which is supported by reports and experiments, is inappropriate gastrointestinal magnesium loss(81). Thus, the reduction in intestinal acidity due to PPIs impairs intestinal luminal magnesium absorption by causing dysfunction of transient receptor potential melastatin (TRPM6) protein channels(82). If this is true, PPI may cause slow depletion of magnesium stores over time; thus, it may explain the long period it takes to develop hypomagnesemia that was evidenced in previous studies. This point has important implications for patients who have a depleted magnesium store, such as the elderly, those who are suffering from malnutrition, and individuals who are taking additional

medications that cause low magnesium because these individuals are likely to be at a greater risk of developing hypomagnesemia.

Table 1-2: observational studies that have reported an association between the use of PPI and hypomagnesemia

Reference	Year	Study design	Population studied (No. of all patients)	PPI use status (No. of PPI users)	Outcome definition	Results
Gau et al(83)	2012	Cross-sectional	Hospitalized patients (487)	Current user (207)	Hypomagnesemia defined as serum Mg levels less than 1.7mg/dL	Adjusted OR for hypomagnesemia 2.50 (95%CI 1.43 to 4.36)
Faulhaber et al(84)	2013	Cross-sectional	Hospitalized patients (151)	Current user (56)	Serum Mglevels	No difference (p-value=33) between the mean of serum Mg levels of PPI users(1.97±0.2) and non-users (2.00±0.2)
Danziger et al(85)	2013	Cross-sectional	Hospitalized patients (11,490)	Current user (2,632)	Hypomagnesemia defined as serum Mg levels less than 1.6mg/dL	Adjusted OR for hypomagnesemia 1.10 (95%CI 0.96 to 1.25)
Koulouridis et al(86)	2013	Nested case-	Hospitalized patients (402)	Current user (402)	hypomagnesemia (serum Mg <1.4 mEq/L)	Adjusted OR 0.82 (95% CI 0.61 to 1.11).

		control study				
Markovits et al(87)	2014	Cross-sectional	Community patients (95,205)	Current user(22,458)	Hypomagnesemia defined as serum Mg<0.7 mmol/L	Adjusted OR for hypomagnesemia 1.66 (95%CI 0.55 to 1.78)
Lindner et al(88)	2014	Cross-sectional	Hospitalized patients (5118)	Current user (389)	Hypomagnesemia defined as serum Mg < 0.75 mmol/l	Adjusted OR for hypomagnesemia OR = 2.1 (95% CI: 1.54–2.85).
Zipursky et al (89)	2014	Case control	Community patients (1830)	Current, recent, or remote user (366)	Hospitalization with hypomagnesemia(ICD-10 codes)	Adjusted OR , 1.43; 95% CI 1.06–1.93)
Kieboom et al.(90)	2015	Cross sectional	Community patient (9,818)	Current use	Hypomagnesemia (serum Mg<1.44 mEq/L)	OR for hypomagnesemia 2.00 (95%CI 1.36 to 2.93)
Misra et al(91)	2015	Cross - sectional	Hemodialysis patients(155)	Current use (55)	Mean of serum Mg	Serum Mg levels were significantly lower among PPI users vs. non-users (0.93 vs. 1.02 mmol/L, p < 0.0001)

Begley et al(92)	2016	Both cross-sectional and cohort	Community patients 156 patients	Cross section: Long term use 100 patients	Mg level in blood at baseline	serum Mg levels (P = 0.39)
				Cohort: new PPI user (56)	repeat blood and urine Mg measurements at basline,2, 4 and 8 months	no significant difference in the mean Mg levels

PPI: proton pump inhibitor, Mg: magnesium, OR:Odd Ratio, CI: Confidence Interval, P: P value

1.5.2. The Use of PPIs and Increased Susceptibility to Infection:

Susceptibility to infection among PPI users has received increasing attention in recent years, and this particular side effect has become more controversial than the other negative outcomes linked with PPI usage. Lab studies have reported that gastric acid has a potent bactericidal effect at pH<4, which is capable of killing ingested bacterial pathogens(93). Stomach acid is believed to play an important role in preventing infections(93,94). As such, reducing the production of gastric acid and instigating a state of hypochlorhydria may increase the risk of bacterial infection. This effect is considered to represent the main biologically plausible mechanism for the link between PPI and infection that the published studies have identified. The majority of these studies have explored two types of infection: pneumonia, which is an infection of the lung tissue(95), and Clostridium difficile (C. difficile) infection, a bacterial infection that infects the bowel and causes diarrhoea. In the case of pneumonia, researchers have suggested that the above mechanism causes colonisations of pathogens in the upper gastrointestinal tract and subsequent translocation to the respiratory system, which leads to increased risk of pneumonia(96). Alternative evidence has suggested the

presence of H/K ATPase proton pump in the mucus cells in the respiratory tract where it is possible for PPI to alter the pH of the seromucinous secretions, thus leading to the increased risk of pneumonia(97,98). On the other hand, a reduction in gastric acidity helps enteric pathogens to escape local gut defences and cross the epithelial barrier of the intestine(99). Animal model studies have shown that the use of PPI encourages the growth of the gut microflora due to acid inhibition, increases bacterial translocation, and alters other anti-inflammatory and immunomodulatory effects in the intestine(99,100).

The following section provides a brief overview of the studies that have examined the extent to which PPI users are susceptible to pneumonia and C. difficile infection.

1.5.2.1. Community-acquired pneumonia

Pneumonia, is a common cause of morbidity and mortality especially among the elderly and those with other medical comorbidities(101). Studies that have assessed the risk of pneumonia in patients treated with PPI have gradually shown a largely coherent pattern of moderately increased risk of hospital-acquired pneumonia in critically ill patients(102,103). For community-acquired pneumonia, the existing evidence

from observational studies has yielded conflicting conclusions(104–111). Concern was however amplified by findings from meta-analyses based on these observational studies that showed that the risk of community-acquired pneumonia was between 34% and 49% higher among patients that use PPIs than it was among nonusers, and that the risk increased as the dose of PPI increased (96,112–114)(Table 1-3).

However, the observational studies involved in those meta-analyses have been criticised on the basis that they lack control for unmeasured confounding(115), such as patient characteristics and comorbidities, and bias(116), such as confounding by indication, which may influence the significance of the association. In addition, a strong temporal relationship between the use of PPI for less than seven days and an increased risk of pneumonia have been reported(96), while the association was weak among PPI users who had been taking PPIs for a longer duration, which is contrary to what one would expect if PPIs increase the risk of community-acquired pneumonia. Jena et al. examined the role of confounding in the association between PPI use and community-acquired pneumonia by estimating whether PPI use is also associated with other illness that are unrelated to

PPI use(e.g., urinary tract infection, deep vein thrombosis)(115). They found that PPI use is also associated with an increased risk of other medical conditions and suggested that the observed relationships between PPI use and pneumonia may be confounded by unobserved patient and physician characteristics among users of PPIs. On the contrary, a cohort study examined this association using a restricted cohort of NSAID users who were taking PPIs across eight routine databases, which avoided confounding by indication and protopathic bias, found no increased risk of hospitalisation for community-acquired pneumonia compared with nonusers (116). So far, few studies analysed data from the original safety trails of omeprazole and esomeprazole. These studies reported no increase in the risk of pneumonia in patients receiving those classes of PPIs compared to those treated with a placebo or other acid suppressive medications(106,117).

Therefore, given the limitations of previous studies, the evidence about the association between increased community-acquired pneumonia risk and PPI use remains questionable because residual confounding may have contributed to the relatively modest increased risk observed in the previous studies.

Table 1-3 Published meta-analyses on the association between PPI use and risk of community-acquired pneumonia

Reference	Year	Number of studies included	Odds ratio of the risk community-acquired pneumonia with PPI (95% CI)
Johnstone et al,(112)	2010	6 observational studies	1.36 (95%CI 1.12 to 1.65; I^2 92%)
Eom et al,(96)	2011	8 observational studies	1.34 (95%CI 1.14 to 1.57; I^2 93.6%)
Giuliano et al,(114)	2012	9 observational studies	1.39 (95%CI 1.09 to 1.79; I^2 97%)
Lambert et al,(113)	2015	26 observational studies	1.49 (95%CI 1.16 to 1.92; I^2 99.2%)

95% CI: confidence interval
I^2 index of heterogeneity

1.5.2.2. Clostridium difficile Infection

Through the mechanisms mentioned earlier, PPIs appear to increase a patient's susceptibility to enteric infection including Salmonella, Campylobacter jejuni, and C. difficile(99,118). The association between PPIs and C. difficile infection has been more comprehensively recorded than other potential associations with enteric infection. The majority of the studies on this topic were hospital-based with the exception of the few that looked for community-associated C. difficile infection(119–121). While some studies have reported no association between PPI use and C. difficile infection, others have concluded an increased risk of C. difficile infection (122,123). Those studies have been combined in two meta-analyses, the results of which showed a significant increase in the incidence of C. difficile infection among patients on PPI therapy with an overall risk estimate of between 1.65 (95% CI 1.41 - 1.93)(124) and 1.74 (95%CI 1.47-2.85) (125). This caused sufficient concern that the US FDA issued a drug safety report that warned users that PPIs may be associated with C. difficile infection(126).

To date, no randomised placebo-controlled trials have been conducted to solidify the causality of this effect because the

associated ethical issues and challenges related to the rarity of the outcome to be studied in such trials entails that conducting such studies is challenging. It remains unclear if the reduction in acid secretion in patients who use PPI on a long-term basis is an independent risk factor associated with the increased risk of C. difficile infection, or whether potential confounders, such as comorbidities, can explain the observed associations

1.6. Outline and objectives of the thesis

As illustrated by the review above, most of the evidence supporting the adverse effects of PPIs is observational, and they have not 'pushed the data' hard enough to really tease out whether the observed relationships between PPI use and pneumonia are confounded. Demonstrating the effect of these confounders on the association between PPI use and the potential adverse effects, especially those of interest related to community-acquired pneumonia, is important to determine whether observed associations between PPI use and pneumonia are likely to be causal or reflect unmeasured factors. In addition, the proposed mechanism of PPIs that may have induced the increased risk of infection have yet to be fully clarified, and further research is required in this area. Before investigating the association between PPI and infection in depth, it would be useful to illustrate a specific aspect of the

current use of PPIs and the extent to which existing guidelines are applied in general practice. Therefore, this thesis aims to examine the pattern of PPI use in the general UK population before investigating the role of confounding in the association between PPI use and an increased risk of community-acquired pneumonia, and exploring the role of hypochlorhydria as the suggested mechanism of this association. As general practitioners in the UK play an important role in the process by which PPIs are prescribed to patients, the research conducted in this thesis was based on routinely collected electronic healthcare data from UK-based primary care practices.

1.6.1. Chapters outline

An overview of the chapters included in this thesis is as follows:

Chapter 2: Database and overview of study designs. In this chapter, a description of the database that was used in this project is provided together with an overview of the study designs employed. Detailed methods of the relevant studies are included in subsequent chapters.

Chapters 3-5: Each chapter addresses one of the main objectives of the thesis. The chapter commences with a background to the study before progressing to describe the methods in detail. The results of the analysis are then

presented followed by a discussion of the findings in relation to the existing literature.

The following are the objectives that each of the chapters addresses:

- Chapter 3:

Determines the prevalence and trends of PPI prescription in general practice.

Investigates how many patients who are prescribed PPIs are able to reduce the dose or switch to an alternative treatment in general practice.

- Chapter 4:

Determines whether the association between PPI use and a risk of community-acquired pneumonia can be explained by confounding.

- Chapter 5:

Determines whether the mechanism that PPIs induce increased risks of pneumonia and Clostridium difficile diarrhoea is supported by the same mechanism acting in another cause of achlorhydria (Pernicious Anaemia) with an intact stomach.

Finally, the last chapter summarises the main findings of the thesis before highlighting the clinical consequences of these findings and presenting recommendations for further studies that are based on the outputs of this research.

Chapter Two

Database and Overview of Study Designs

2.2. Introduction

Every UK resident is entitled to access to a general medical practitioner (GP), under the universal National Health Service (NHS) (1). GPs, therefore, administer care for most non-emergency medical conditions, and provide onward medical referrals to secondary care for input as necessary. GPs routinely record and code their patients' data into computer systems during patient's appointments in the form of primary care medical records. These records have helped to construct a primary care database that captures the important health information that is stored within patients' records and provides useful data about the diagnosis, prescription history, and therapeutic interventions of this large population.

Because of its size and comprehensiveness such a database can be particularly useful when searching for uncommon outcomes and/or attempting to develop an understanding of drug treatment usage in clinical practice. A routine data source of this nature can also be employed to provide insights into the use and effects of drugs in the general population because of its unselected nature.

This chapter describes the Clinical Practice Research Datalink (CPRD) data that was used in the research presented in subsequent chapters and explains how the exposure to PPIs

was defined. It also provides an outline of the study designs employed and how the data was assessed within each study.

2.3. Clinical Practice Research Datalink (CPRD)

2.3.1. Database Description

The CPRD is a large, longitudinal database that consists of primary care medical records from the computer systems of participating general medical practices across the UK(127). It was first established in 1985 as the Value Added Medical Products(VAMP) central Data Bank(128). In 1993, it was renamed the General Practice Research Database (GPRD), and in 2012, it expanded further to become the CPRD(129–131). The CPRD is currently managed by the MHRA and is jointly funded by both the NHS and the MHRA(131). The CPRD contains anonymised electronic clinical records of the data entered by GPs of over 681 contributing general practices that have agreed at practice level to provide the data to the CPRD, however, at individual level patients can be excluded from data load if the patient insists on opting out(127,129,131). Each patient at the participating practice has a unique record and each time he or she visits the GP a new consultation record is opened with an associated date. This allows the GP to enter details related to the patient's consultation including symptoms, diagnoses, prescriptions, investigation requests,

test results or any referrals together with basic demographic and lifestyle information. Information about hospital admissions and their outcomes is also entered into the patient's record.

The data are coded using the Read code system (132) to describe a patient's condition, symptoms, medical history, investigations, and any administrative processes that are relevant to the patient's treatment. The medications prescribed by the GP are automatically recorded for each prescription and the information obtained includes product name related to British National Formulary (BNF) code, dose instructions, daily quantity, and the number of packs/pack size prescribed. Therefore, the prescription information that is stored within the CPRD can allow researchers to perform a reliable assessment of drug use. The results of laboratory tests are added to the patient's record and, since 2005, 90% of CPRD practices use electronic test recording (133).

2.3.2. Advantages and limitation of CPRD

After the data are entered by GPs, comprehensive data quality checks are undertaken to ensure the information is of a satisfactory quality. Data quality markers have been determined at both the practice and patient level(129,131).

Reaching the practice-level quality assessment standard is referred to as "up to standard" (UTS) on CPRD(129). The date at which the data entered by the GP is deemed to be UTS is based on two concepts: assurance of continuity in data recording and monitoring of mortality rate. The patient level quality assessment is flagged by an "acceptable" registration status through a process that identifies and excludes patients with poor data recording that question the validity of a patient's record(129).

By its very nature, CPRD GOLD provides a rich resource of data in terms of size, duration, and data quality. In July 2013, the CPRD held data from over 681 practices across England, Wales, Scotland, and Northern Ireland, covering approximately 11.3 million patients, which represented 6% of the UK population in terms of age and gender distribution(131). It included over 79 million person-years of follow-up with an overall median follow-up of 5 years (131), thereby allowing researchers to study long-term outcomes.

The database has been widely used in research, and studies that have sought to validate the CPRD diagnosis have determined that it has a high positive predictive value for a wide range of diagnoses (134,135). However, Read code lists need to be developed for each study to identify exposures and

outcomes of interest as there are no generally standardised definitions for diagnoses, or in some cases researcher can build on previous code lists using the ClinicalCodes repository(136).

Although the CPRD represents a highly valuable resource for drug safety research, some relevant information about the patient's medical needs and pharmaceutical usage may not be captured on individual records. For example, the use of over the counter (OTC) medications and secondary care prescriptions. In addition, missing data about important variables, such as smoking, alcohol consumption, and Body Mass Index(BMI), may limit the information gained from such variables. However, in 2004, the Quality and Outcomes Framework (137) was introduced to encourage medical practitioners to record key variables, such as smoking status, and this has subsequently improved the extent and depth of the data stored in the system(131,138,139).

2.3.3. Linkage

CPRD GOLD has access to a number of linked datasets including the Hospital Episode Statistics (HES), the Office for National Statistics (ONS) mortality data, the Index of Multiple Deprivation(IMD), the Townsend scores (deprivation data),

and other disease registry data (127). The data contained in the HES consists of information about all hospitalised care, outpatient appointments, maternity care, and critical care at NHS secondary care hospitals (140). The diagnosis data recorded in the HES and the mortality data are based on the coding defined in the International Classification of Diseases (ICD) 10th revision(127).

An encrypted and anonymised unique patient identifier is generated by a third party, and allows records for each patient to be identified and linked together. Over 50% of the CPRD practices have agreed to participate in the CPRD linkage scheme to provide patient-level information(131). It is has been shown that the population in the linked dataset is representative of the UK population apart from some exceptions (e.g temporary residents)(141).

With the exception of the first study, all remaining studies in this project employed the subset of the CPRD with HES data as a secondary analysis to utilise the advantages of hospital diagnosis and admission dates (increase the sensitivity and specificity of measuring outcome and a higher possibility of avoiding misclassification).

2.3.4. CPRD data files

2.3.4.1. CPRD GOLD

CPRD GOLD data is provided in the form of ten files that can be linked using the encrypted patient identifier(patid). The ten files are the patient file, practice file, staff file, consultation file, clinical file, additional clinical details file, referral file, immunisation file, test file, and therapy file. Table 2-1 describes the structure of the basic CPRD GOLD files that were employed in this project.

2.3.4.2. HES data file

The HES data is arranged into files relating to hospitalisation, which refers to the total period of an in-patient's hospital stay. Each hospitalisation has one or many "consultant" episode(s) of care, which correspond to the period during which patients were under the care of one consultant. Each episode has an admission date, a discharge date, and duration of hospitalization in days. For each episode, up to 20 diagnoses and 24 procedures may be recorded, and the diagnosis data recorded are coded using the ICD-10 clinical coding and procedural coding is based upon UK Office of Population, Census and Surveys classification (OPCS4)(127).

A source file is provided that allows the identification of the subset of CPRD GOLD patients who are eligible to have a record in the HES data during the available HES years. These files can be linked to corresponding GOLD patient cohort file using the encrypted patient identifier. A linkage coverage file provides the start and end dates of the HES encounter time.

Table 2-1: the description of the structure of the basic files from CPRD GOLD

CPRD-GOLD file	Information contained
The patient file	one row of data per patient that includes the patient's date of birth, gender, registration date with the practice, date of transfer out of the practice, death date, and variable indicating acceptable patient status.
The practice file	One row of data per practice identifier with date of last collection for the practice, and date of UTS.
The clinical file	One or multiple rows per patient) for each event with the date associated with the event and unique code for the event for medical term selected by GP.
The therapy file	One or multiple rows per patient containing the detail of prescriptions issued in primary care, which also comprises the issue date of prescription, drug substance, numeric daily dose, daily quantity and the number of packs/pack size. British National Formulary (BNF) is the classification system used in this file.
The test file	One or multiple rows per patient for investigation and laboratory tests that have been requested for the patients together with the date of the test when requested and the result value
Additional file	Additional information such as lifestyle and preventative health care. Data in this file is linked to events in the clinical file.

2.4. Data extraction

The Independent Scientific Advisory Committee (ISAC) of the MHRA approved the protocols for the studies in this PhD thesis (Protocol reference numbers 13_214, 13_215R, 15_240R).
I employed the CPRD_August_2013 version of the GOLD database from which I have extracted the data for the studies presented in this thesis. This data consisted of approximately 15 million patients from 678 practices. The CPRD provide data dictionaries and coding dictionaries that researchers can use to create code lists. CPRD provides software tools known as the "Code Browser" in which various search terms were used to find codes. I used the BNF code dictionary to create lists for the PPI exposure, and other medication variables. The Charlson Comorbidity Index(142) code lists were constructed by Dr Colin Crooks, and I employed this to calculate the index score for the purpose of producing some of the analyses contained in this thesis.

2.4.1. Data management for calculating the prescription length of prescribed PPI

PPI prescriptions were defined by therapy prodcodes according to the BNF, Section 1.3.5(31),which include omeprazole, lansoprazole, esomeprazole, pantoprazole and rabeprazole.

The prescription length of PPIs were calculated based on the dosage instructions. The therapy file contains some recorded dosage instructions that allows calculation of the length of each prescription in days. The available recorded data include the number of treatment days recorded by the GP, the total quantity prescribed, numeric daily dose prescribed, and the total quantity entered by the GP. These data were not completely recorded for all patients, therefore, we used a systematic method to calculate individuals' therapeutic course for those patients who had missing data as described below. The earliest PPI prescription for each patient was defined as the patient's index date. The duration of each prescription was taken as the number of treatment days recorded by the GP, or calculated by dividing the total prescription quantity by the numeric daily dose prescribed for each prescription if both variables were recorded. If the numeric daily dose value was missing but the prescription quantity was recorded, the patient's prior prescription records were used to compute the missing values. Otherwise, the individual median duration was used to determine the missing duration where both the numeric daily dose and prescription quantity were missing. If the calculated prescription duration was less than seven days, the prescription quantity was presumed to refer to the number

of individual product packs prescribed, and the prescription duration was recalculated accordingly.

2.5. Overview of study designs and analyses

The following section provides a brief summary of the study designs and analyses employed in this PhD research. Details of the methods involved in the individual studies are included in the relevant chapters.

2.5.1. The prevalence and trends of PPI prescription in general practice.

All patients who were issued with ≥1 PPI prescription during the period 1990–2013 were identified. The annual prevalence of PPI was calculated for the study period. Additionally, new users of PPI therapy who had five years of follow-up data were included in a cohort to describe the current use of PPIs in terms of the patterns of cessation and duration of use.

2.5.2. PPI use and risk of community acquired pneumonia study

In this chapter, I examined the association between community-acquired pneumonia and PPI prescription. Adult patients who were newly prescribed a PPI (exposed) were selected and individually matched, according to age, gender and year of prescription, with those who had not been

prescribed PPI (un-exposed). We used three methods in this study:

(1) A multivariate Cox model that compared the risk of the first occurrence of community-acquired pneumonia in PPI-exposed patients in comparison to controls, corrected for potential confounders,

(2) A self-controlled case series analysis(143) to calculate the incidence rate ratio (IRR) comparing the incidence rate of community-acquired pneumonia during the exposure period with the incidence rate during the baseline period ,and

(3) A prior event rate ratio (PERR)(144,145) analysis by dividing the unadjusted hazard ratio for pneumonia during the year after initial PPI prescription (of the exposed group versus the unexposed group) by the unadjusted hazard ratio for pneumonia before the PPI prescription (of the exposed versus the unexposed group).

2.5.3. The risk of Clostridium Difficile Colitis and community-acquired pneumonia in persons with pernicious anaemia

This is a retrospective cohort study conducted in CPRD and utilising linked HES data where available. The exposed group were patients who have a diagnosis of pernicious anaemia and who had been treated with vitamin B12 therapy. Exposed patients were matched with ten non-pernicious anaemia

patients in terms of age, gender, and general practice. Pneumonia and Clostridium difficile were the primary outcomes in this study. Cox regression analysis was used to determine the hazard ratio(HR) for the associated outcome with pernicious anaemia. Potential confounders were controlled in the Cox regression analysis.

Chapter Three

The Prevalence and Trends of PPI Prescription in General Practice.

3.1. Introduction

This chapter reviews the existing studies on PPI use in primary care. It then progresses to describe the detailed methods for calculating the prevalence rate of PPI prescriptions among all eligible adult patients in the CPRD, and the cohort analysis that was performed to identify patterns of cessation and duration of PPI use. After that, the results for the prevalence estimate of PPI use during the study period and the pattern of PPI prescription are presented. The chapter concludes with a discussion of how the results of the current study compare to the research findings described in existing literature. This study was carried out using data from the CPRD_August_2013.

This study was approved by the ISAC (protocol number 13_214). The findings described in this chapter have been published in a peer-reviewed journal(146). We used CPRD GOLD July 2015 to extract the data for the analysis presented in the published paper as we extended the study period to the year 2014 upon the reviewer's request (ISAC protocol number 13-214Mn).

3.2. Background to study

The upward trend of PPI use and the cost of the total prescription also appears to be associated with an inappropriate utilisation of these drugs and the long-term use of PPIs(43,50,147). As a consequence, clinical guidelines in the UK have endorsed recommendations to control PPI use in the primary care setting. The NICE provides guidance on the management of patients with dyspepsia in the UK and recommends that prescriptions of PPI are rationed, either by stepping down the dose or stopping treatment all together(7). Few studies have examined the extent to which the clinical guidelines are being followed in the UK and, of those that do, many have not estimated how many patients took PPI on a long-term basis. These studies described the pattern of PPI use over a limited time frame(47,52,53) or certain geographical areas (52,53) and the definition of long-term PPI use was not clear(54). In addition, no studies have examined very recent national trends in PPI use in the community setting, the trend in indications for their use, and the management of long-term prescriptions. Given the continuous increase in the prevalence of PPI use and the concerns surrounding the long-term use of these drugs, general practitioners need to continually reassess the appropriateness of PPI utilisation. The aim of this study, therefore, was to

determine the prevalence of PPI use and assess the practices employed to reduce PPI use in the general UK population. It is anticipated that research of this nature will help to inform future attempts to moderate the use of PPIs and reduce the cost this incurs.

3.3. Method

3.3.1. Study population:

This descriptive study includes two analyses: repeated cross-sectional analyses to estimate the prevalence of PPI use annually, and a cohort design to describe the patterns of cessation and duration of use.

The source population included all adult patients in the CPRD between 1 January 1990 and 1 August 2013. Subjects were considered eligible for inclusion if they had one month of registration on CPRD after the date of their current registration or the date after the practice became UTS on CPRD, whichever was the latest; known gender; and an "acceptable" patient registration status(129). Subjects who were registered temporarily with the practice were excluded. This population formed the denominator for the prevalence studies that were performed as part of this analysis. Patients who received ≥1

PPI prescription during the defined study period were classified as exposed subjects in the study (i.e., the numerator).

3.3.2. Prescribing patterns for PPI

To describe the use and management of the long-term therapy of PPIs in general practice, we identified a cohort of new users of PPI therapy; i.e., patients with at least 12 months of registration on CPRD prior to the first date of PPI prescription and who had a minimum of five years of prospective follow-up data after the index date. Any prescription date issued after five years from the index date was excluded from this analysis.

As mentioned in Chapter 1, the NICE guidelines describe the management of several underlying causes of dyspepsia in primary care and provide guidance on the appropriate prescription of PPIs. These guidelines were used to determine what constitutes expected long-term PPI use within this study(Table 1-1)(7).

Exposure to PPI in this group was defined as commencing at the index date and ending at the date on which the last prescription was expected to have been used up within a period of continuous prescriptions. Prescriptions were

considered continuous if the gap between the end date of the preceding prescription and the start date of the next prescription was less than or equal to 30 days. If a new prescription was issued before the end date of the previous prescription, it was assumed that the on-going prescription ended on the date the new prescription began (Figure 3-1). One set of continuous prescriptions was defined as one course. Each PPI course was then classified as either short (<12 months) or long (≥12 months). Individuals who received exclusively short courses were classified as short-term users, while individuals who received at least one long-term course were classified as long-term users, even if their records contained additional short-term courses.

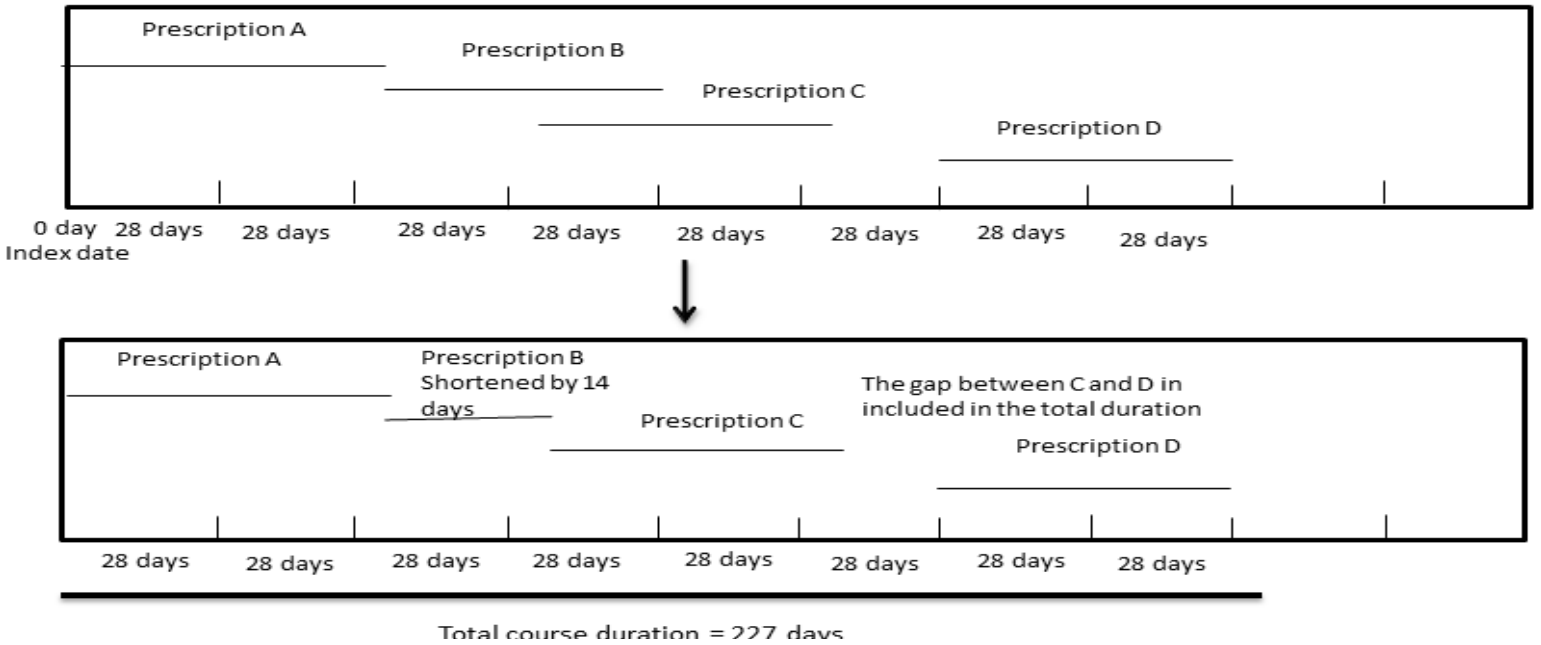

Figure 3-1 Schematic diagram illustrating how the prescription are shortened and connected to calculate overall course duration for each patient

Discontinuation was defined as no subsequent PPI prescription issued within 30 days after the end of the last PPI prescription. Discontinuation was categorised as temporary (if patients were subsequently re-prescribed PPI) or permanent (if no further prescriptions were received up to the end of patient's follow-up). A step down of PPI therapy was defined as a reduction in the daily dose of the subsequent PPI prescription. If a subsequent prescription was for a different PPI, the dose was converted to an equivalent dose based on the recommended doses of different PPIs for the same indication,(BNF, Section 1.3.5(31)). A successful step down was defined as maintaining the stepped-down dose for 12 months from the step-down date. The NICE guidelines(7) recommend that patients who are prescribed PPI on a long-term basis undergo an annual review, at a minimum, to consider withdrawal or step down the treatment dose; therefore, step-down attempts in long-term patients that were maintained 12 months after the initial step down were deemed to be successful. Finally, a switch to H2RA medication was defined as receiving H2RA prescription within one month of the discontinuation or stepping down attempt.

3.3.3. Other Covariates

Covariates included patients' age at the index date in 10-year age bands, gender, and socioeconomic status (derived through linking CPRD to the Index of Multiple Deprivation (IMD) 2007). For each PPI course, the potential indications for treatment were identified by referring to the Read codes for dyspepsia, GORD, gastritis, duodenitis or peptic ulcer coded on the first prescription date, if available, for each PPI course from the linked clinical file (list of codes included in Appendix 1). In patients who had no indication recorded on the first prescription date, had their medical file searched for any recorded potential indications within 12 months after that date. We considered the prevention and treatment of NSAID-associated ulcers the indication if the NSAID prescription date fell on the same date as the PPI prescription. Potential indications were then classified into eight categories (Table 3-1). Missing initial indications were recorded as a separate category and co-prescribed NSAID drugs were included in the NSAID prophylaxis category.

Table 3-1Categories of potential indication for proton pump inhibitor prescription

Potential indication category	Description
Dyspepsia	Dyspepsia in addition to other symptoms (epigastric pain, indigestion, stomach upset)
Uncomplicated GORD	Heartburn, esophagitis
Complicated GORD	Barretts oesophagus, oesophageal strictures and stenosis, ulcer of oesophagus
Peptic ulcer below oesophagus	Including complicated and un complicated gastric and duodenal ulcer(acute/chronic)
NSAID prophylaxis	Non-Steroidal Anti Inflammatory drug induced gastric ulcer Anti-platelet induced gastric ulcer
Helicobacter therapy	Helicobacter gastritis, Helicobacter breath test positive
Reduction of pancreatic enzyme degradation	Cystic fibrosis and chronic pancreatitis
Gastritis & duodenitis	Acute or chronic gastritis/duodenitis without mention ulcer, gastric erosion

GORD= Gastro-oesophageal reflux disease; NSAID nonsteroidal anti-inflammatory drug

3.3.4. Statistical analysis:

3.3.4.1. Estimating prevalence of PPI use:

For each year we calculated the period prevalence by dividing the number of patients who received at least one PPI prescription during that year by the corresponding mid-year adult population of the CPRD. We also calculated annual point prevalence as the number of patients with an ongoing PPI prescription on 30th June divided by the corresponding mid-year population. We stratified these prevalence estimates by gender and age (calculated on June 30th and grouped into 10 years age bands).

3.3.4.2. Patterns of PPI use

The baseline patient characteristics and the use of PPIs among new users were described as proportions of age bands, genders and quintiles of IMD (to represent socioeconomic status). We calculated the percentage of patients who continued their first PPI course, from the index date to the end of five years of follow-up during the study period.

Kaplan Meier survival curves were constructed among all new PPI patients to graphically describe: 1) time to discontinuation (permanent or temporary) of the first PPI course during the five years follow-up, 2) time to permanent discontinuation of all PPI therapy during the five years follow-up. Time to

discontinuation of the first PPI course was calculated from the index date to the first PPI course's end date. Time to permanent discontinuation was calculated from the index date to the end date of the last PPI course that each patient received during the follow-up period.

The proportions of patients, who stepped down, or substituted PPIs were calculated for long-term users as NICE guidelines recommend reviewing long-term PPI users on an annual basis at a minimum(7). To determine successful step down attempts accurately patients were required to have 12 months of available data after the step down date. The analysis of successful step down attempts was therefore limited to patients who had stepdown attempts within the first 4 years of the 5 year follow-up to allow adequate time for follow up within the final year of the cohort. We repeated this analysis restricted to patients who started PPI therapy as long-term and whose indication might not suggest an ongoing need for long-term PPI use, therefore patients with a recorded indication of complicated GORD, NSAID-associated ulcers prophylaxis or to reduce the degradation of pancreatic enzyme supplements were excluded.

3.4. Results

3.4.1. Prevalence of prescribing

We identified 27,004,699 PPI prescriptions in 1,638,639 adult patients during the study period. The point and period prevalence of PPI increased between 1990 and 2012 (Figure 3-2) and it varied substantially by age group (Figure 3-3). The point prevalence of PPI use was similar between males and females, increasing during the study period from 0.04% in 1990 to 6.5% in 2012 in males, and from 0.03% in 1990 to 7.7% in 2012 in females (Figure 3-4). The female to male prevalence ratio of PPI use was 1.14 (95% confidence intervals (CI) 1.11-1.17) from 1990 to 2012.

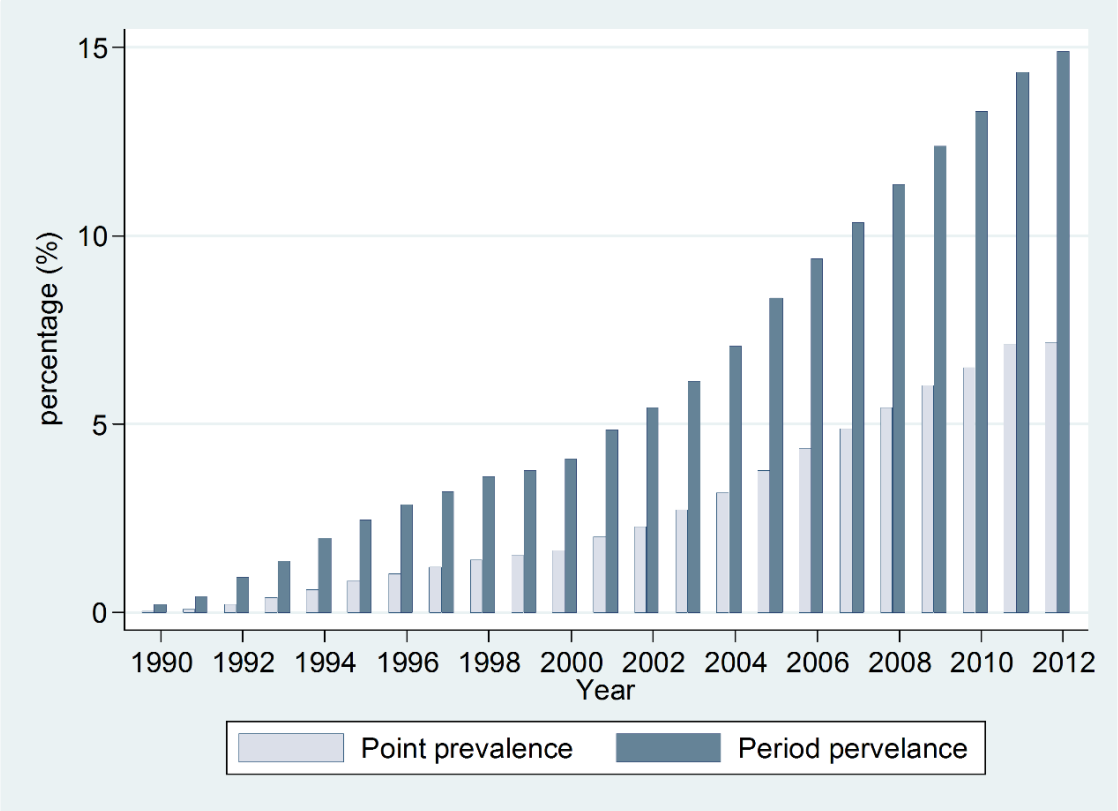

Figure 3-2 Point and period prevalence (%) of proton pump inhibitor(PPI) use during the period 1990–2014 in adult CPRD population.

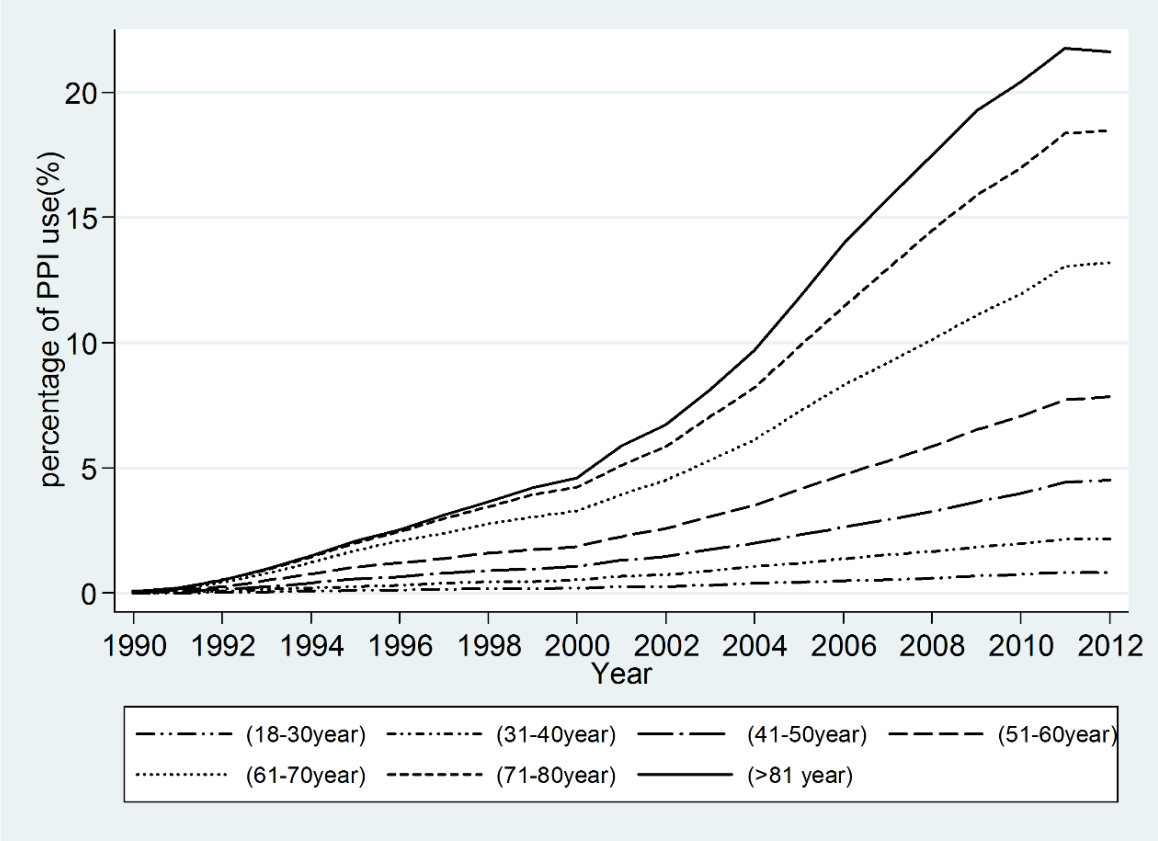

Figure 3-3 Point prevalence (%) of proton pump inhibitor(PPI) use by age in 10-year age band during the period 1990–2014 in adult CPRD population.

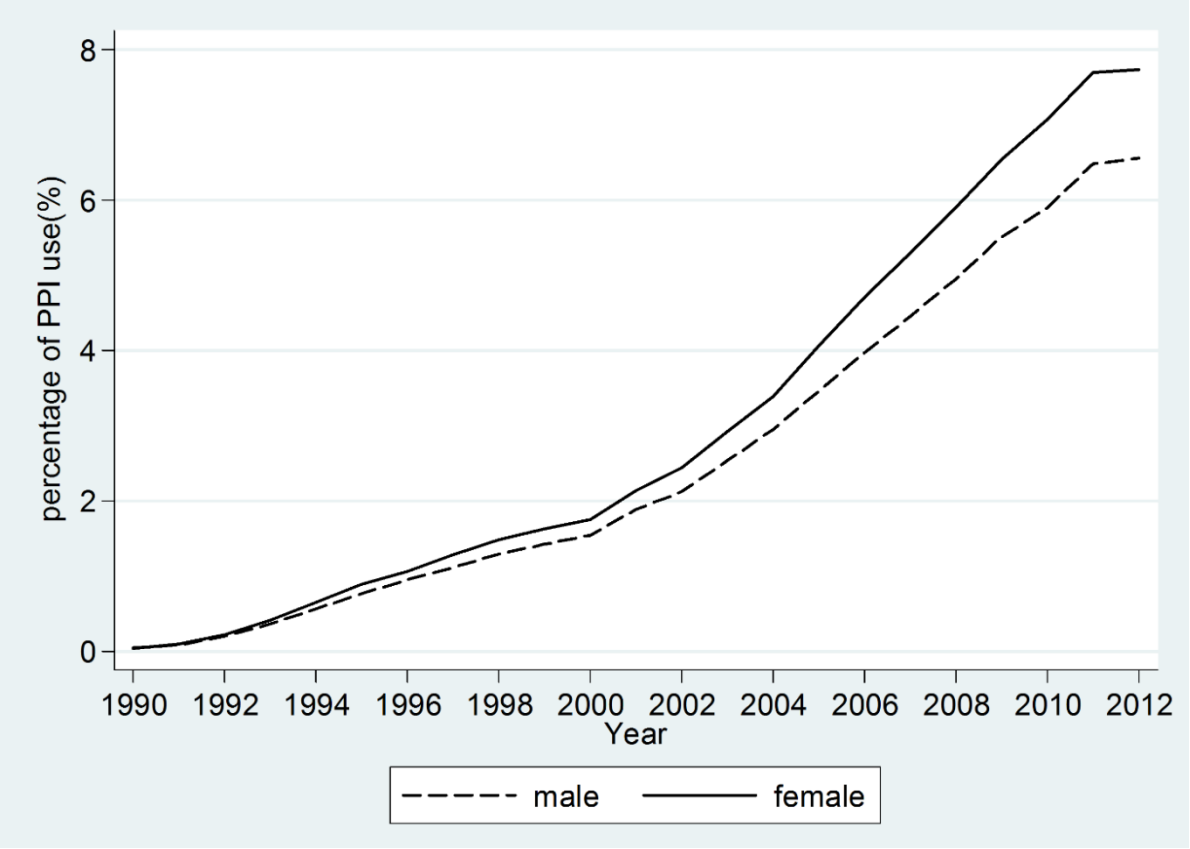

Figure 3-4 Point prevalence (%) of proton pump inhibitor(PPI) use by gender during the period 1990–2014 in adult CPRD population.

3.4.2. Prescribing patterns

During the study period, 504,190 new users of PPI therapy with at least five years of follow-up data were identified. Their mean age was 54.4 years (Standard Deviation SD: 16.3) and 55% were females. They received a total of 7,579,356 prescriptions and 132,421 patients (26.2%) had one PPI prescription recorded. The median duration for all PPI prescriptions was 28 days (interquartile range (IQR) 28-56 days)(Figure 3-5).

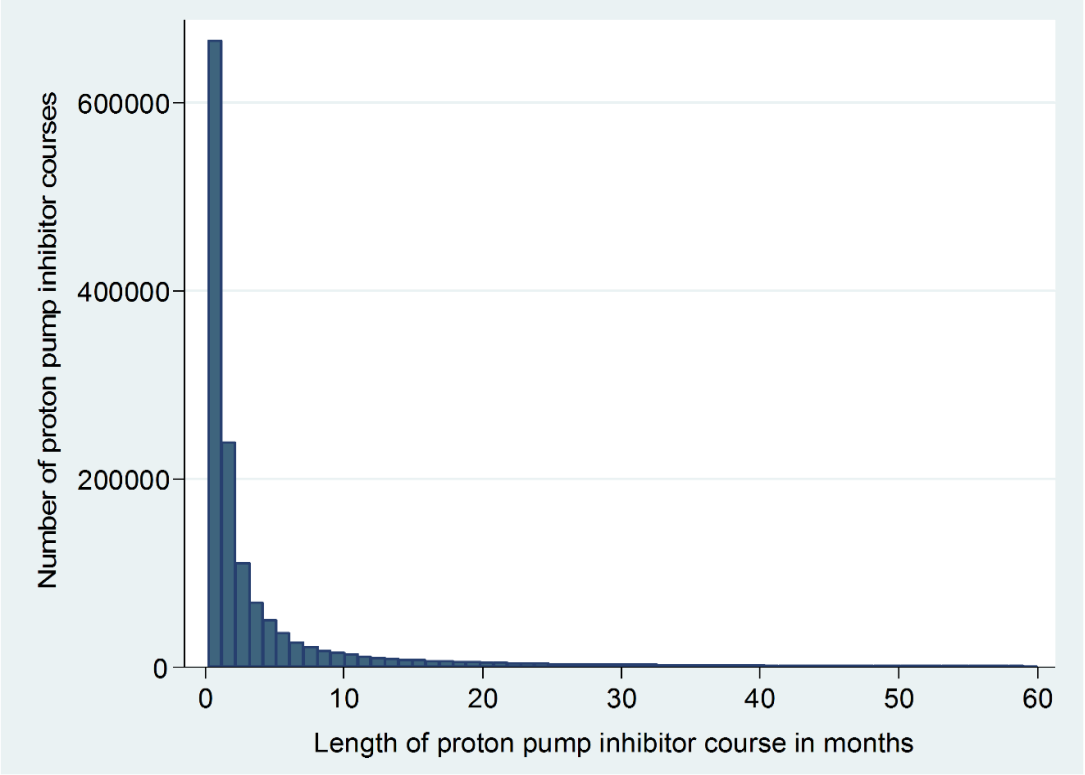

Figure 3-5 Duration of all proton pump inhibitor courses in months during the 5-year follow-up.

Individual prescriptions were combined to create 1,454,863 PPI courses. The median duration of all courses was 56 days (IQR 28-127 days) and there were a median of 2 courses per patient (IQR 1-4 courses). Patients received prescriptions for enough PPI to cover 96.65% (95%CI 96.63-96.66) of days in these courses.

1,278,944 (87.9%) of the courses were categorised as short courses and 175,919 (12.0%) were categorised as long courses with median durations of 28 days (IQR 28-81 days) and 806 days (IQR 526-1350 days) for short and long courses respectively (Figure 3-6 & Figure 3-7). 72.7% of the cohort received exclusively short courses with a mean age of 51.7years (SD 16.3 years), and 27.3% received at least one long course with a mean age of 61.3years (SD 14.3 years)(Table 3-2). Within this cohort, 194,241patients (38.5%) had only one PPI course, and 309,719 (61.4%) patients had multiple courses. Around 16.7% and 11.7% of patients remained continuously on PPI therapy for 6 and 12 months from their index date, respectively. At the end of 5 years of follow-up, 22,256 (4.4%) patients had remained on PPI continuously from the index date.

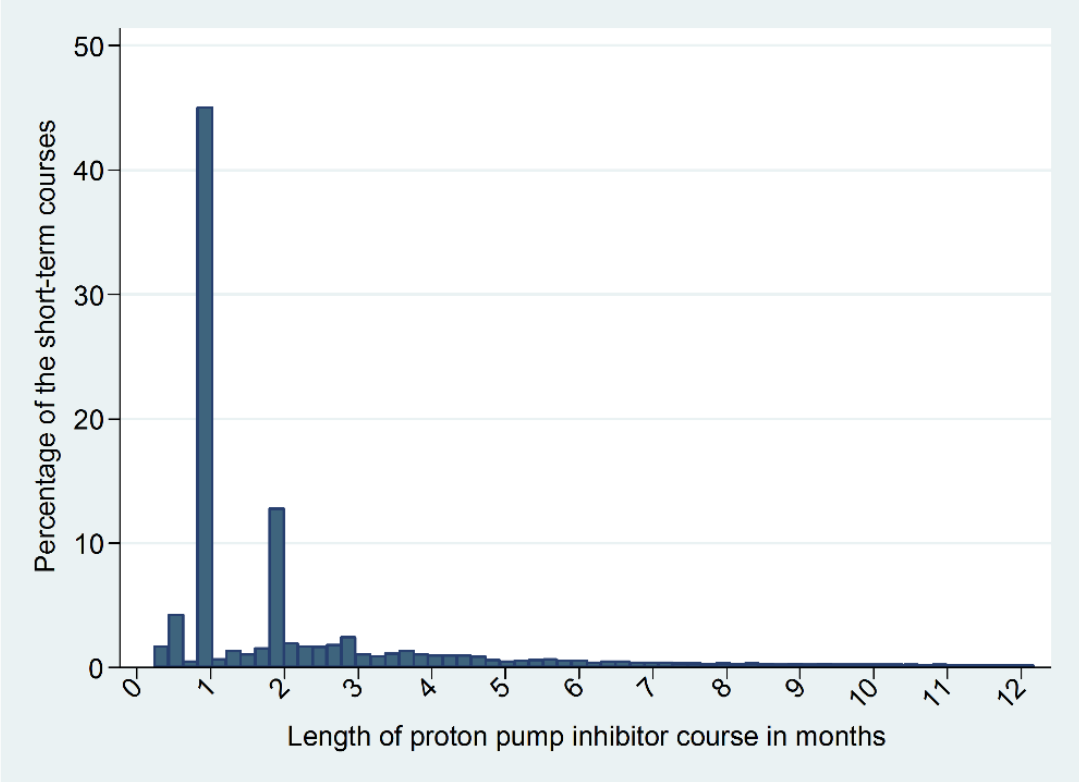

Figure 3-6 Duration of short courses among new users of PPI therapy with at least five years of follow-up data.

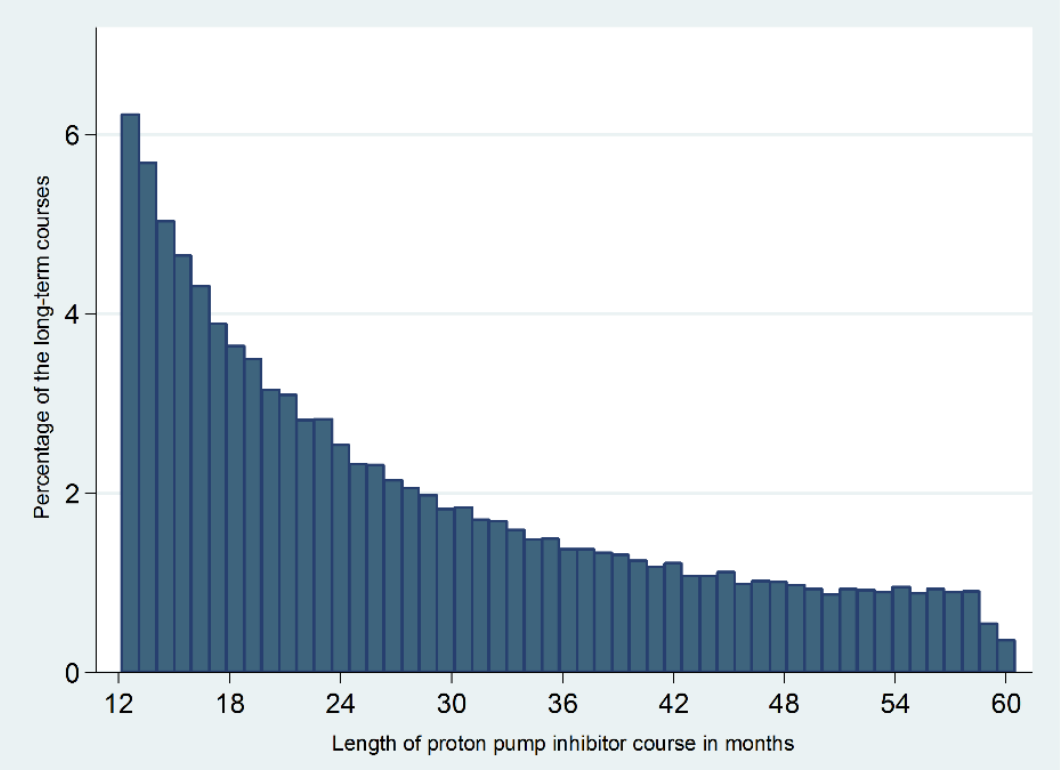

Figure 3-7 Duration of long-term courses among new users of PPI therapy with at least five years of follow-up data.

Table 3-2 Descriptive characteristics of new users of proton pump inhibitor (PPI) therapy with ≥ 5 years of follow-up data (patients with exclusively short- term courses and patients with at least one long-term course), and the duration (in days) for the first short and long courses.

	Total number		**Patients with exclusively short course**			**Patients with at least one long course in their records**		
Patients characteristics	N=504,190		N=366,546		Duration of first short course	N=137,644		Duration of first long course
		%	Number	%	Median(IQR)	Number	%	Median(IQR)
Age								
18-30	41,046	8.1	38,020	92.6	28(28-28)	3,026	7.3	711(491-1197)
31-40	71,088	14.1	61,525	86.5	28(28-48)	9,563	13.4	770(503-1324)
41-50	95,131	18.8	76,311	80.2	28(28-56)	18,820	19.7	814(525-1413)
51-60	102,721	20.3	73,107	71.1	28(28-56)	29,614	28.8	878(545-1501)
61-70	100,531	19.9	63,787	63.4	28(28-56)	36,744	36.5	937(567-1571)
71-80	69,635	13.8	40,803	58.6	28(28-57)	28,832	41.4	981(583-1617)
>80	24,038	4.7	12,993	54.0	28(28-61)	11,045	45.9	1012(590-1660)

Gender								
Male	222,129	44.0	160,274	72.1	28(28-56)	61,855	27.8	924(559-1563)
Female	282,061	55.9	206,272	73.1	28(28-56)	75,789	26.8	886(547-1503)
Index of Multiple Deprivation (quintiles)**								
Unavailable	220,401	43.7	158,434	71.8	28(28-56)	61,967	28.1	910(554-1540)
1(least deprived)	63,968	12.6	48,032	75.0	28(28-56)	15,936	24.9	866(538-1478)
2	67,137	13.3	49,163	73.2	28(28-56)	17,974	26.7	895(549-1519)
3	56,984	11.3	41,426	72.7	28(28-56)	15,558	27.3	911(559-1537)
4	55,154	10.9	40,058	72.6	28(28-56)	15,096	27.3	908(557-1537)
5(most deprived)	40,546	8.0	29,433	72.5	28(28-53)	11,113	27.4	903(555-1564)

IQR=interquartile range

** Socioeconomic status is based on Index of multiple deprivations (IMD) .

3.4.3. Prescription indications

Initially, 282,776 PPI courses (19.4 %) had no coded indication for PPI prescription. This fell to 13.8% after assuming prescriptions concurrent with NSAID prescriptions were intended for gastro-protection. Dyspepsia was the most frequent recorded indication(Table 3-3).

Table 3-3 Recorded indication for all proton pump inhibitor(PPI)courses(all short courses in exclusively short-term PPI users and all long courses in patients with at least one long-term PPI course)

	Total number		**Patient with exclusively short courses**		**Patients who had at least one long-term course**	
	N=504,190		**N=366,546**		**N=137,644**	
Indication category	All PPI courses 1,454,863	%*	Short PPI courses 978,001	%*	Long PPI courses 175,919	%*
Dyspepsia	532,626	36.6	393,126	40.2	40,706	23.1
un-complicated GORD	432,948	29.7	268,207	27.4	62,710	35.6
NSAID prophylaxis	97,001	6.7	63,365	6.5	14,498	8.2
Gastritis &duodenitis	109,128	7.5	62,910	6.4	20,454	11.6
peptic ulcer below oesophagus	46,485	3.2	25,375	2.6	9,416	5.4
Helicobacter therapy	20,983	1.4	16,108	1.7	1,322	0.8
GORD complicated	11,646	0.8	4,878	0.5	2,587	1.5
Reduction of pancreatic enzyme degradation	3,020	0.2	1,635	0.2	499	0.3
missing	201,026	13.8	142,397	14.5	23,727	13.4

* column percentage; GORD= Gastro-oesophageal reflux disease; NSAID nonsteroidal anti-inflammatory drugs

3.4.4. Discontinuation, step-down, and substitution

Figure 3-8 shows the proportion of patients who discontinued the first PPI course, and patients who permanently discontinued all PPI courses (Figure 3-9). When considering only long-term PPI patients, 25% had temporarily discontinued their therapy at one year and two months after starting their long-term PPI course, 50% at one year and six months and by two years and three months 75% had temporarily discontinued their long term PPI course. Of those discontinuing, 8,723 (10%) received a prescription for H2RA within one month before or after this occurred.

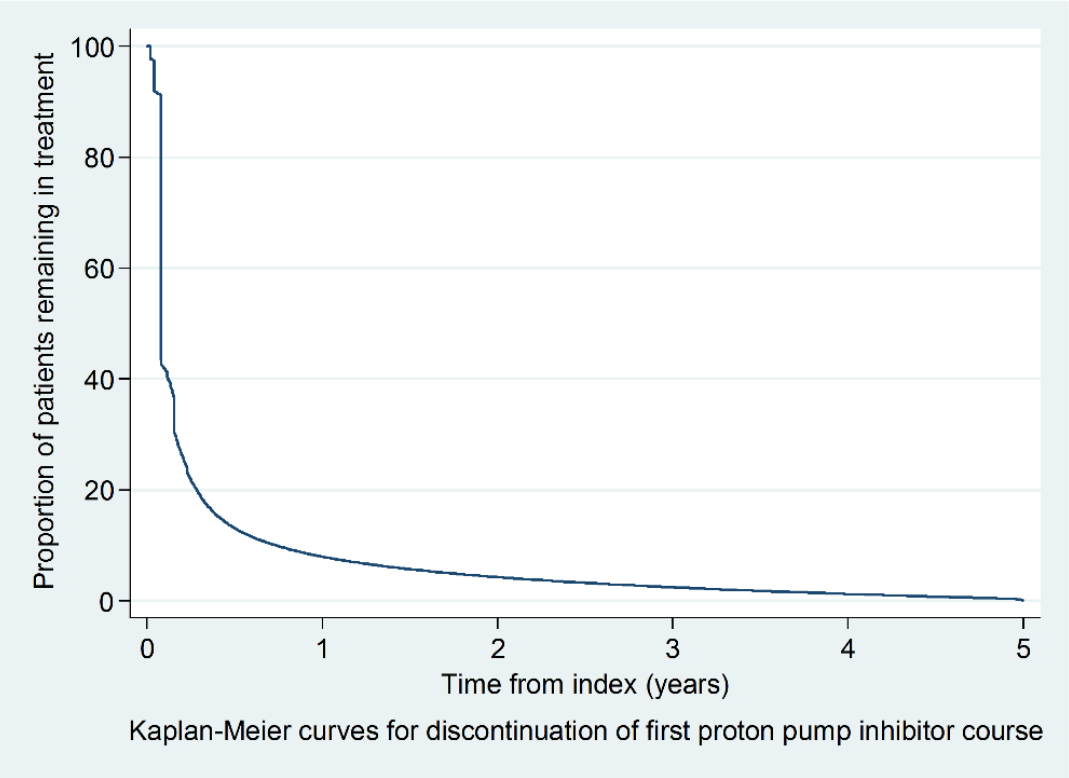

Figure 3-8 Kaplan–Meier curves for time to discontinuation of the first proton pump inhibitor (PPI) course (permanent and temporary) during the 5-year follow-up.

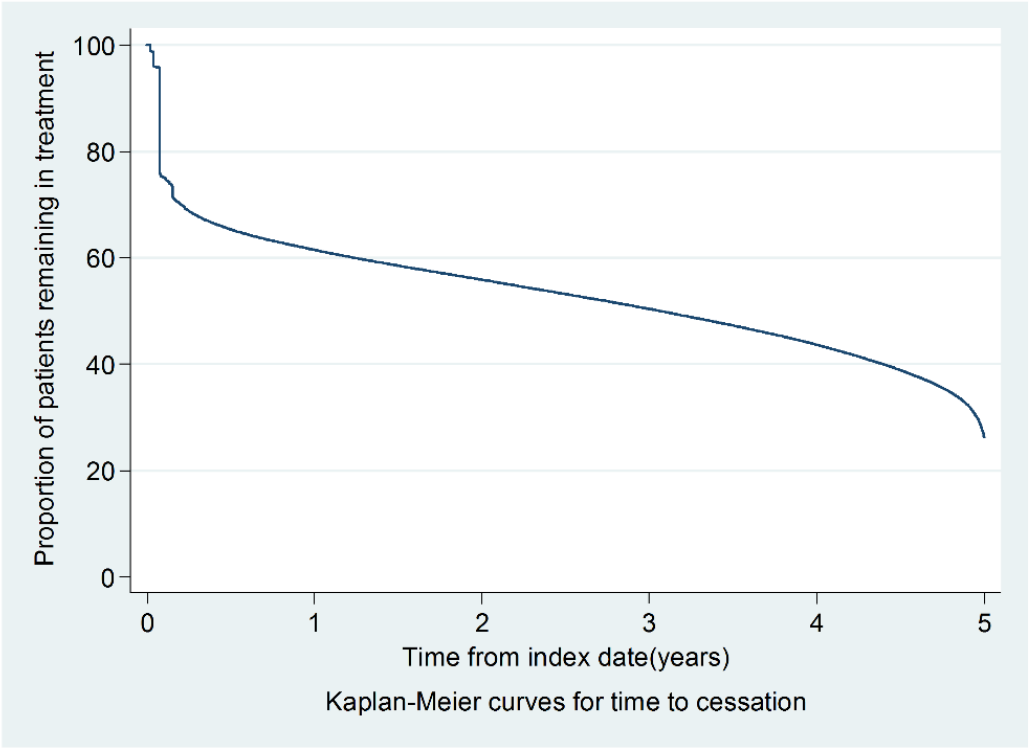

Figure 3-9 Kaplan–Meier curves for time to permanent discontinuation of all PPI therapy during the 5 years of follow-up (total number of patients 596 334). At the end of 5 years of follow-up, 22,256 (4.4%) patients had remained on PPI continuously from the index date, while 110,301 (21.8%) patients were on PPI therapy from a subsequent PPI course.

Of the 137,644 patients who received long term PPIs, 56,918 (41%) had an attempt to step down their PPI dose (Table 3-4). Of these 5,906 (10%) had received an H2RA prescription within one month before or after stepping down PPI dose.
Of 52,118 patients in whom the initial indication for PPI prescription did not suggest a recognised need for PPI use to be prolonged, un-complicated GORD was the most frequent recorded indication and 34,098 (65.4%) discontinued PPI therapy (temporarily or permanently). For those patients who temporarily discontinued their PPI therapy the median time to this was 3 years and 3 months after starting their PPI course. In those using PPI long term without recognised indication for such use a step down attempt was identified in 48% (Table 3-5).

Table 3-4 Numbers and percentages of long-term proton pump inhibitor (PPI) users who attempted a step down in dose, were successful at 12 months, and were prescribed histamin2 receptor antagonists (H2RA) by age, time, and indication.

	Patients with at least one long PPI course	Number of patients who had step down to lower PPI dose		Number of patients who maintained lower dose after step down attempt for 12 months**		Number of patients who received H2RA substitution at time of step down and /or discontinuation	
		Number	%*	Number	%	Number	%*
	137,644	56,918	41.3	32,089	60.3	12,753	9.2
Age group							
18-30	3,023	1,343	44.4	590	46.9	274	9.0
31-40	9,552	4,273	44.7	2,072	51.8	812	8.5
41-50	18,799	8,092	43.0	4,183	55.4	1,403	7.4
51-60	29,580	12,603	42.6	6,970	59.1	2,393	8.0
61-70	36,854	15,349	41.6	8,748	61.0	3,713	10.0
71-80	28,814	11,304	39.2	7,015	66.2	3,037	10.5
>80	11,022	3,954	35.8	2,511	67.9	1,121	10.1
Time when GP attempt to step down							
2 months		22,425	39.4	16,374	73.1	3,682	16.4

6 months		12,962	22.7	7,311	57.6	1,600	12.3
12 months		8,166	14.3	3,463	45.9	1,104	13.5
More than 12 months		13,365	23.4	4,941	46.7	1,799	13.4
Indication							
GORD un-complicated	49,166	23,942	48.7	13,272	59.0	5,646	11.4
Dyspepsia	31,835	13,192	41.4	7,757	63.0	2,911	9.1
Gastritis &duodenitis	16,307	7,134	43.7	3,307	50.3	1,814	11.1
NSAID prophylaxis	10,987	3,002	27.3	2,144	75.6	460	4.1
peptic ulcer below oesophagus	7,428	3,550	47.7	2,128	63.4	731	9.8
GORD complicated	1,944	619	31.8	355	61.3	115	5.9
Helicobacter therapy	1,053	377	35.8	200	56.3	87	8.2
Reduction of pancreatic enzyme degradation	370	117	31.6	53	48.6	26	7.0
missing	18,554	4,985	26.8	2,873	62.4	963	5.1

GORD=Gastro-oesophageal reflux disease; NSAID= non-steroidal anti-inflammatory drugs H2RA=Histamine 2 Receptor antagonist

*percentages were calculated from the total number of long-PPI patients

** percentages were calculated from the number of step down patients who stepped down within the first 4 years of follow-up and successfully stepped down for 12 months (number of patients (53,189))

Table 3-5 Numbers and percentages of long-term proton pump inhibitor (PPI) users who attempted a step down in dose, were successful at 12 months, and were prescribed histamin2 receptor antagonists (H2RA) by age, time, and indication. Analysis restricted to indications unsuitable for step down.

	Patients with at least one long proton pump inhibitor course	Number of patients who had step down to lower PPI dose		Number of patients who maintained lower dose after step down attempt for 12 months**		Number of patients who received H2RA substitution at time of step down and /or discontinuation	
		Number	%*	Number	%	Number	%*
	52,118	25,270	48.4	15,196	61.5	5,108	9.8
Age group							
18-30	898	490	54.5	238	48.9	105	9.7
31-40	3,093	1,710	55.2	862	51.1	299	8.3
41-50	6,585	3,349	50.8	1,869	56.7	593	7.7
51-60	10,901	5,490	50.3	3,187	59.3	1,003	8.0
61-70	14,162	6,867	48.4	4,180	62.2	1,603	9.8
71-80	11,737	5,367	45.7	3,513	67.3	1,413	10.6
>80	4,742	1,997	42.1	1,347	69.4	551	10.1

Time when GP attempt to step-down							
2 months		10,409	41.1	7,444	71.5	2,019	17.4
6 months		6,218	24.6	3,744	60.2	2,339	6.0
12 months		3,087	12.2	1,513	49.0	433	12.7
More than 12 months		5,556	21.9	2,495	50.0	776	12.5
Indication							
GORD un-complicated	19,698	11,112	56.4	6,597	60.4	2,323	11.7
Dyspepsia	11,905	5,726	48.1	3,652	65.2	1,158	9.7
Gastritis &duodenitis	6,876	3,373	49.5	1,757	53.4	732	10.6
peptic ulcer below oesophagus	3,739	1,951	52.1	1,253	65.7	371	9.9
Helicobacter therapy	349	170	48.7	101	60.1	32	9.1
missing	9,551	3,373	30.7	1,836	64.7	492	5.1

GORD=Gastro-oesophageal reflux disease; H2RA=Histamine 2 Receptor antagonist
* percentages were calculated from the total number of long-PPI patients
** percentages were calculated from the number of step down patients who stepped down within the first 4 years of follow-up and successfully stepped down for 12 months(number of patients (24,703)

3.5. Discussion

3.5.1. Summary

This study describes the pattern of PPI prescription in UK general practice in terms of its prevalence and the practices employed to reduce long-term use. The proportion of the population using PPIs within each year increased from 0.2% in 1990 to 14.8% in 2012. Of those new PPI users who had five years of follow up available, the majority of patients use a PPI for a short period, 27.3% used PPI therapy for more than one year, and 4.4% remained on PPI therapy for five full years. Clear attempts to step down long-term use were identified in about 41%, and 9% of long-term users received a H2RA prescription around the time they attempted to step down and/or discontinue their use of PPI. Amongst patients whose initial PPI prescription indication did not necessarily warrant long term PPI use, 48% had attempts to step down their PPI dose.

3.5.2. Comparison with previous work

Our findings pertaining to the prevalence of PPI use in the early years of our study were consistent with the findings of earlier studies involving general practice in the UK(3,23-25). In 2005, a study estimated period prevalence of PPI use of 8% among those younger than 65 years(41), which was consistent

with the findings of our study. In addition, we found that the use of these drugs has continued to rise since. The overall trend of increased PPI prescribing over the study period may be attributed to the continuous use of PPIs to replace H2RAs for the management of acid-related disorders(149) and to an increasing number of patients treated with long-term PPI (150). These trends are not limited to the UK: similar increases in prescription rates have been observed in the United States(45), Australia(42), and many European countries(150,151). This widespread increase supports the evidence that PPI prescriptions remain highly prevalent in many healthcare systems, despite the extensive literature that indicates PPI has been overprescribed in both the primary and secondary care settings(46,149,152).

In this study, the proportion of patients who were on long-term PPI (27%) was higher than that described in previous studies(53,54,148), which have reported rates of long-term PPI usage between 0.05% and 4.4%, according to varying definitions of long-term use. However, a recent cohort study found that the proportion of long-term first-time users (defined by redemption of >60 defined daily doses of PPI within six months) increased from 27% in 2001 to 37% in 2011, indicating an increase in the proportion of long-term PPI

users(151). Adding to this, studies have shown that repeat prescription practices account for approximately 32 to 81% of the total cost of prescribed drugs(153). The continuous increase in PPI use, specifically the rise in the proportion of long-term users, may, therefore, have important cost implications despite the availability of low-cost PPI.

PPIs provide effective symptomatic relief for patients who suffer from dyspepsia symptoms. However, while clinical guidelines suggest the use of PPI therapy over short durations to treat dyspepsia symptoms(7), it seems that PPIs had been prescribed as a form of maintenance therapy without specific underlying cause. Our study revealed that dyspepsia symptoms were the initial indication in 23% of long-term PPI courses. However, as most patients on first presentation in primary care will not have a final endoscopic diagnosis, it is inevitable that the GPs will have recorded less-specific indications in subjects who had other underlying diagnoses. Our results concur with those of several studies that have reported that the majority of patients on PPI therapy are prescribed PPI for the purpose of relieving symptoms without any other clear indications(43,151,154). A recent study estimated an increase in the rate of first-time users between 2001 to 2011 in which around 96% of their long-term users did not have a recorded indication to use PPI therapy(151). In

addition, although the clinical relevance of rebound acid hypersecretion after withdrawal of PPI therapy has been the subject of much debate in the existing literature. It has been proposed that the rebound acid hypersecretion following PPI therapy withdrawal may help perpetuate the use of PPIs in patients with uncertain indications or who have received them for symptomatic relief of relatively mild symptoms for more than six weeks (155).

The issue of appropriateness in terms of prescription practices has been discussed in existing literature(151,152,156,157). Several factors might influence the prescribing pattern of PPIs. Some studies have suggested that patient's medical factors in terms of morbidity and co-medication and socio-economic factors influence the initiation and maintenance of long-term PPI therapy(151,158). Other studies have shown that the characteristics of the prescribing general practice influence the management of their patients. Haastrup et al. examined the association between general practice characteristics and prescribing PPIs and concluded that there is significant variation in initiating PPI therapy between practices and that some of this variation is associated with GP characteristics such as age and gender(159). Despite this, PPIs are still being administered to patients for a variety of complaints that are

not known to be acid-induced and for long-term basis. Enhancing rational prescription of PPIs could prevent some patients from suffering avoidable adverse effects and save the healthcare system significant amounts of money.

In view of the emerging concerns regarding adverse events from long-term PPI use, clinical guidelines(7) have encouraged GPs to use PPIs carefully and to continually review long-term patients to try to step down or stop treatment. Our results suggest that GPs are actively attempting to reduce PPI use by stepping down and substituting alternative medication. Previous studies(157,160–162) reported discontinuation rates that differed from those identified in our study; however, these can be explained by variations in the study population and the discontinuation strategies employed(161). Reports regarding the outcomes of step-down therapy have been conflicting(163,164). For example, one study reported that more than half of the patients involved in the study remained asymptomatic after the step down(164) while another reported that 19% of patients whose PPI therapy was stepped down experienced relapsed symptoms and resumed PPI use(163). In our study, 60% of the long-term PPI users maintained lower doses for more than one year. However, while we identified an appreciable proportion of long-term PPI

users who could potentially reduce the use of the drug, we were unable to find evidence of such attempts in a large proportion of those individuals. Non-adherence to the step down of therapy, therefore, allows the maintenance of inappropriate PPI prescription which may sustain overuse of PPIs.

3.5.3. Strengths and limitations

Our study used data from a large database of UK primary care records which has been extensively used and validated for pharmacoepidemiological research(129,134). The population in our study is therefore representative of the general practice population of the UK to whom our results should be generalizable(129). The large sample size has allowed us to stratify our analyses by age groups and gender, and to show trends in PPI use over time. It has also provided us with adequate power to identify the relatively small proportion of patients who took PPIs on a long-term basis and describe the management of their prescriptions in UK primary care.

Weaknesses in our study include that we may have underestimated PPI use since neither hospital prescriptions nor OTC use are captured in the data. However, since secondary care initiated PPI treatment will often be continued by GPs afterwards(156), and prescribed PPI use continued to rise

after they became available OTC (165) we think it unlikely that this has led to substantial underestimation. Additionally, we focused on long-term users who would be the most likely to obtain their prescriptions from their GPs.

Furthermore, the period of PPI exposure for those who took PPI intermittently may have been underestimated, since the calculation of the prescription duration was based on the assumption that the dispensed prescription was consumed as directed. Indeed, CPRD only contains information about the prescriptions of medications; as such, it is not possible to assess whether patients actually collected or consumed the prescribed medication. On the other hand, since our definition of continuous PPI use allowed a 30-day gap between prescriptions to be included in the total duration of the PPI course, the duration of continuous use in some subjects may have been overstated.

In addition, our definition of a successful stepdown may underestimate the proportion of patients whose long-term PPI therapy was stepped down but then required a small increase in dose to one still lower than the initial dose. However, including this in our definition only identified an additional 909 patients (an additional1.6% of attempted step downs) so for

clarity we retained our initial stricter definition. Furthermore, our method of estimating successful step down attempts within the initial 4 years of follow-up would not have led to a substantial underestimation, as it is expected that long-term patients should have been offered a step down attempt at least within the first year of their continuous use of PPI therapy.

3.6. Conclusion

During the study period, a considerable increase in the administration of PPI prescriptions was observed in UK general practice. The majority of patients use PPIs on a short-term basis with 27% of the identified use long term. Our results suggest that GPs are actively attempting to decrease the use of PPI by stepping down and discontinuing prescriptions; however, this is not universally practised, nor is it always successful when attempted. There were still an appreciable proportion of long-term PPI users in whom attempts to reduce or cease use might be appropriate, and in whom we were unable to find evidence of such attempts. If the cost and potential risks of the continuing increase of PPI are to be minimised, a proactive clinical review and adherence to the guidelines is likely to be required.

Chapter Four

Community-Acquired Pneumonia Incidence Before and After Proton Pump Inhibitor Prescription: A Population-Based Study.

4.1. Introduction

This chapter begins by introducing the prior event rate ratio (PERR) adjustment method as a new approach to reduce the bias that results from unmeasured confounding in observational studies. This method has been applied to assess the potential effect of PPIs on community-acquired pneumonia risk alongside other methods (Cox regression analysis and self-controlled case series analysis). The incidence of community-acquired pneumonia before and after the use of PPIs are presented followed by a discussion of the findings.

This study was approved by the ISAC (protocol number 13_215R). The findings presented in this chapter have been published in a peer-reviewed journal(166).

4.2. Prior event rate ratio adjustment method

In observational pharmacoepidemiology studies conducted in large health care utilisation databases, bias due to different unrecorded baseline risks for diseases in exposed and unexposed cohorts cannot be completely ruled out, as it is not possible to allocate treatment by chance as is the case in randomised control trials. However, they do represent the best sources that are available for studying the association between prescribed medications and rare potential adverse outcomes

that cannot be identified in smaller random controlled studies. Several approaches have been proposed to address the effect of unmeasured confounders in health care database studies(167). More recently, an analytical method, the PERR adjustment method, has been applied as a means of reducing the bias that results from this residual confounding (144,145,168).

The PERR adjustment method relies on a before and after design. The underlying assumption of this method in pharmacoepidemiology studies is that any differences in outcomes between exposed and unexposed cohorts before receiving the treatment reflect the combined effect of confounders independently of any effect of the study drug(144). This approach is therefore dependent on the fact that neither the exposed or unexposed patients are treated with the study drug before the study commences. The PERR is then estimated by the ratio of two unadjusted HRs: the HR for the outcome after starting the treatment (the exposed group relative to the unexposed group (HR.post)) and the unadjusted HR for outcome before receiving the treatment (the exposed group relative to the unexposed group (HR.prior)).

PERR adjusted hazard ratio=HR.post/HR.prior (Figure 4-1).

Therefore, the PERR provides an estimate of the effect the drug exposure had on the hazard, adjusted for both measured and unmeasured confounding assuming this dose not change over time (144) .

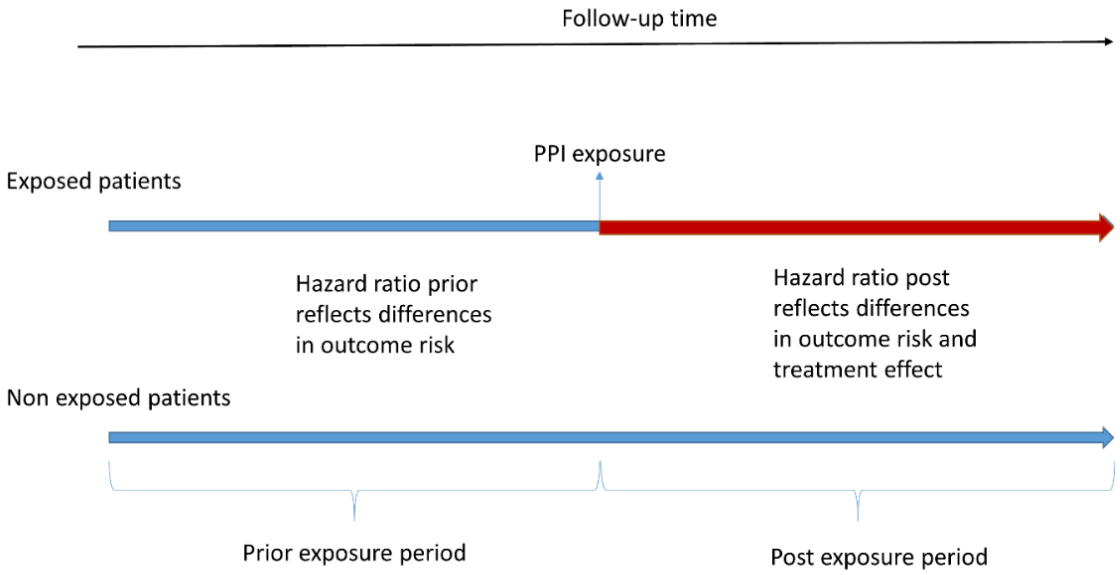

Figure 4-1 Prior event rate ratio (PERR) adjustment method. Prior period means time before index date (proton pump inhibitor (PPI) prescription date for exposed cohort and matched date for unexposed patients); post period means time after PPI exposure.

This approach was first described in 2008 by Tannen and colleges who employed this technique to mitigate some of the effects of hidden confounding in the analysis of time-to-event data that was contained in electronic medical record databases(144,168,169). In their first study, data from CPRD were used to replicate the Scandinavian Simvastatin Survival Study of evaluation of simvastatin in hypercholesteraemic patients with coronary heart disease(169). They reported that the use of the PERR method to adjust the myocardial infarction outcome yielded a result similar to the randomised control trials. Then, by using the same data, the research group replicated two randomised controlled trials of angiotensin-converting enzyme inhibitors in patients without congestive heart failure (168). This was followed by a broader validation of PERR by comparing cardiovascular outcomes from previously performed randomised controlled trials with database studies that replicated those trials(144). Thus, they replicated existing randomised control trials by identifying cohorts from a clinical database using the same inclusion and exclusion criteria, study period, and similar treatment of the trials with the exception of randomisation. They reported that the PERR-adjusted HR was similar to the HR from trials in 11 of 14 outcomes, and demonstrated that, when the Cox adjusted HR(calculated with standard Cox method) from the

database study differed from the result of the trial, the PERR adjusted HR results were much more consistent with the findings of the trial. This suggested that PERR-adjusted results adjusted for the presence of unmeasured confounding.

Since then, a very limited number of studies have employed the PERR to address the effect of hidden confounders in pharmacoepidemiology studies (170). Brophy et al. employed PERR on anonymous GP data to compare the incidence of various gastrointestinal infection infections (Campylobacter and Salmonella infection) in patients prescribed PPIs and those of a set of controls(118). Their results indicated that unmeasured confounders were the main contributors to an increased rate of the infection rather the PPI prescription.

4.2.1. Assumptions and limitations of PERR

Given the promising results that previous research has documented, statistical simulation studies have investigated the PERR adjustment method as a means of characterising the biases from the method, its limitations and applicability(145,171,172). Yu et al. investigated the behaviour of the PERR method and the statistical limits of the PERR method that resulted from simulated studies and compared it to a proposed alternative formulation of the PERR

adjustment method (PERR-ALT). This model used pairwise Cox comparisons of the times to event within the same patients for the prior and post treatment periods; i.e., dividing the HR between the post and the prior treatment periods for the exposed group by the HR between the post and the prior treatment periods for the unexposed group(171). In their simulation studies, they assessed the following; the influence of the prior event on the post event for both exposed and unexposed groups, the degrees of association between the confounders and the exposure, and the variation of the unmeasured confounders with the time intervals(171). The summary of their simulation studies showed the PERR method reduced bias from unmeasured confounding in situations in which the influence of prior events on the study events is small and relatively similar for both exposed and unexposed or when the effect of the unmeasured confounder does not vary by time. In addition, they showed that the PERR-ALT method unsurprisingly could not be performed for rare outcomes, because only subjects with at least one event would be included in the PERR-ALT analysis, which would limit the sample size(171). Recently, a study further examined PERR_ALT approach and showed that the PERR-ALT method is consistent under relevant assumptions; however, the authors confirmed that all models (PERR, PERR-ALT, and Cox model)

are biased if any interaction between treatment and unmeasured confounders takes place or the confounder changes over time (172).

Another simulation study was published in which the authors examined the performance of PERR-adjustment method in several situations(145). They identified many key underlying assumptions for the method to be valid in their simulation study. These assumptions were as follows:

- Constant confounding effect across prior and post periods. Uddin et al. examined the performance of the PERR method when the effect of the unmeasured confounder varied across the two periods and found that, while the PERR method yielded biased estimates, the bias was generally smaller than a conventional Cox analysis(145).
- The prior events should not influence the probability of the subsequent exposure (treatment). Two studies found that the PERR method would produce a biased estimate when the likelihood of the treatment was affected by prior events(145,173). An example of this bias is a study of the effect of statin on stroke, when patients had the first event(stroke) he or she may be prescribed a statin in order to prevent further stroke

events, therefore, the probability of the using statin(exposure) is influenced by previous stroke(event).

- The prior event should not influence the post-event. Uddin et al. showed that the PERR produced biased results when prior events directly influenced the post events and the bias increased when the relation between the both events, prior and post events, was increased(145). For instance, taking mortality/dropout into account, the scale of bias increased as the rate of mortality/dropout increased.

4.2.2. Application of PERR approach to assess the potential effect of PPIs on community-acquired pneumonia risk.

When these assumptions are met, the PERR adjustment method represents an advance from the traditional methods applied to observational research with electronic health care databases. However, when employed in isolation, it will usually not be sufficient to overcome all the scenarios and limitations that challenge its applicability. As a result, previous studies have suggested the use of PERR analysis in combination with conventional biostatistical analyses such as Cox regression analysis. Where similar results are obtained

from different methods these suggest a result is valid, while disparities between methods suggest the presence of unmeasured confounding, in which case the PERR results are more likely to be correct.

I have used the PERR approach in this chapter to examine whether PPI use led to community-acquired pneumonia and assessed the effect of unmeasured confounders on this association. Although existing literature does examine the association between increased pneumonia risk and PPI use, as described in Chapter 1 Section 1.5.1.2, the evidence about this remains questionable. It is important to assess whether confounding explains or doesn't explain the PPI and community-acquired pneumonia relationship, as PPIs are so widely used that any risks will have a considerable impact, while, conversely, incorrectly identified risks may lead to the avoidance of PPIs and could cause harm to the patients. The aim of this study, therefore, was to examine the risk of community-acquired pneumonia and PPI prescription and to assess whether unmeasured confounding explains this association through a combination of methods and sensitivity analyses. Specifically, we used three methods to examine the

association of community-acquired pneumonia with PPI prescription:(1) a multivariable Cox model, (2) a self-controlled case series, and (3) PERR analysis over the 12-month periods before and after the first PPI prescription.

4.3. Method

4.3.1. Identification of study population

The source population for this study included people aged 18 years or over and registered in the CPRD from the 1st of January, 1990, to the 1st of August, 2013. Patients had to have at least one year of registration on CPRD after the latest of the date of current registration and the date the practice became UTS(129) on CPRD, and an "acceptable" registration status as defined by CPRD(129). We identified an exposed cohort from this source population as a random sample of 160,000 of those who were prescribed their first PPI(BNF, Section 1.3.5(31)) in CPRD at least one year after they started contributing data during the study period, i.e. new users. The duration of each PPI prescription was calculated as described in chapter 2 Section 2.3.1.

A subset of patients with linked HES/ONS data were also identified within the study population, and these patients were

selected to improve the ascertainment of the outcome of this study; i.e., community-acquired pneumonia. This has previously shown an improvement in the ascertainment by minimising the selection bias inherent in only using one health care setting to identify outcomes(174). For this subset, we looked specifically at more severe community acquired-pneumonia cases who required hospital admission by limiting the pneumonia definition to those coded within HES/ONS data and the follow-up period was modified to be consistent with the linkage coverage period (from January 1998 to January 2012).

4.3.2. Defining the outcome

We defined community-acquired pneumonia in the CPRD by the presence of a Read code for this diagnosis (Appendix 2). The list included codes for chest and lower respiratory tract infection to ensure that all cases of community-acquired pneumonia categorised in this way were captured. We refer to this as our broad primary care definition and also used a narrow primary care definition eliminating codes not specific for pneumonia. Pneumonia diagnoses recorded less than 84 days apart were regarded as the same event as 84 days were considered sufficient for the clinical condition and lung function to have returned to the baseline state(95,175). For patients with HES/ONS linked data, we identified hospital admission

episodes that were allocated a primary diagnosis of community-acquired pneumonia or a death certificate that was issued between March 1997 and April 2012 on which pneumonia was listed as a contributing or underlying cause of death(based on ICD-10 coding)(Appendix 5).

4.3.3. Study design

Self-controlled case series and cohort study designs were employed in this study.

4.3.3.1. Self-controlled case series study:

The self-controlled case series analysis method is a type of cohort study that was developed to examine the temporal association between the incidence of outcome and a time-varying exposure(143,176). This method was initially used to study the association between vaccines and adverse events; however, it later gained more recognition as a method of studying pharmacoepidemiology(143). Only cases are sampled in this method; i.e., exposed patients who have experienced one or more events during the course of the observation period. As such, the estimates of incidence relate to different periods of exposure within subjects(143,176). The focus of estimation in the self-controlled case series is the incidence rate ratio (IRR), which is the ratio of events in a given

exposure period to the rate of events in the absence (baseline) of the exposure(176). This method, therefore, produces estimates of relative incidence using the Poisson model by conditioning the total number of events and exposures that each individual experienced over a pre-set observation period(176).

The advantage of this design is that the influence of between-individual confounding that remain fixed over the observation period, such as gender, genetics, location, and socio-economic status, will be eliminated(143,176). Time-varying confounders, such as age and calendar year, can be allowed for the baseline incidence. However, this method is based on the following key assumptions:

- The occurrence of an event must not alter the probability of subsequent exposure(176). Thus, there is no short-term dependency between the outcome and the subsequent exposure. Whitaker et al. suggested including a pre-exposure risk period and testing this potential dependency on the basis that a large difference in the IRR associated with this additional pre-risk period would be indicative of the influence of events on the probability of subsequent exposure(176).
- For the method to be valid the event should also not increase censoring or increase the short-term mortality

as this would alter the probability of subsequent exposure. Although Whitaker et al. stated cases in which mortality follows an event are rare, an assumption that is difficult to define, self-controlled case series analysis may be undertaken by setting an observation period to the end of the planned study period(176). An alternative approach to account for this assumption involves excluding subjects who die following an event.

- When modelling multiple events in the analysis, the occurrence of recurrent events must be independent; that is, the occurrence of one event must not alter the probability of a subsequent event occurring(143). The self-controlled case series analysis is suitable in cases of rare and non-recurrent outcomes where, in some situations, the analysis of events that reoccurred may, in itself, be of interest. When there is within-individual dependence, bias from unmeasured confounders that the self-controlled case series analysis sought to reduce is reintroduced.(177). Farrington et al. developed an extension that was specially designed to model the dependence of recurrence times within the context of the self-controlled case series model(177) Two strategies were proposed as a means of dealing with cases in which the validity of this assumption was

uncertain. The first is to limit the analysis to the first event, while the second is to group the repeated events within defined interval into single episodes that can substantially reduce bias in the estimated exposure effect(176,177).

4.3.3.1.1. Application of the method in this study:

From the cohort exposed to PPIs, we selected all the cases with a recorded community-acquired pneumonia. The exposure to PPIs was considered to begin on the date of PPI prescription and end after its calculated duration including any consecutive prescriptions, plus an additional 30-day wash-out period. A 30-day washout period was considered to decrease the likelihood that the exposure periods would be misclassified.

The observation time was then divided into risk windows for each individual (Figure 4-2):

- 30 days before starting the first PPI prescription. The purpose of the additional 30-day period prior to the first prescription was to assess whether any increase in community-acquired pneumonia rate was associated with an acute event that might have precipitated the PPI prescription.
- 0-30 days after starting the first PPI prescription. The primary reason a 30-day period was chosen was that the

median duration of PPI prescription was 30 days (Chapter 3).

- The remaining exposed period with the post-exposure 30-day period.
- The baseline (unexposed) period consisting of all observation times for which no PPI prescription was issued within the study period.

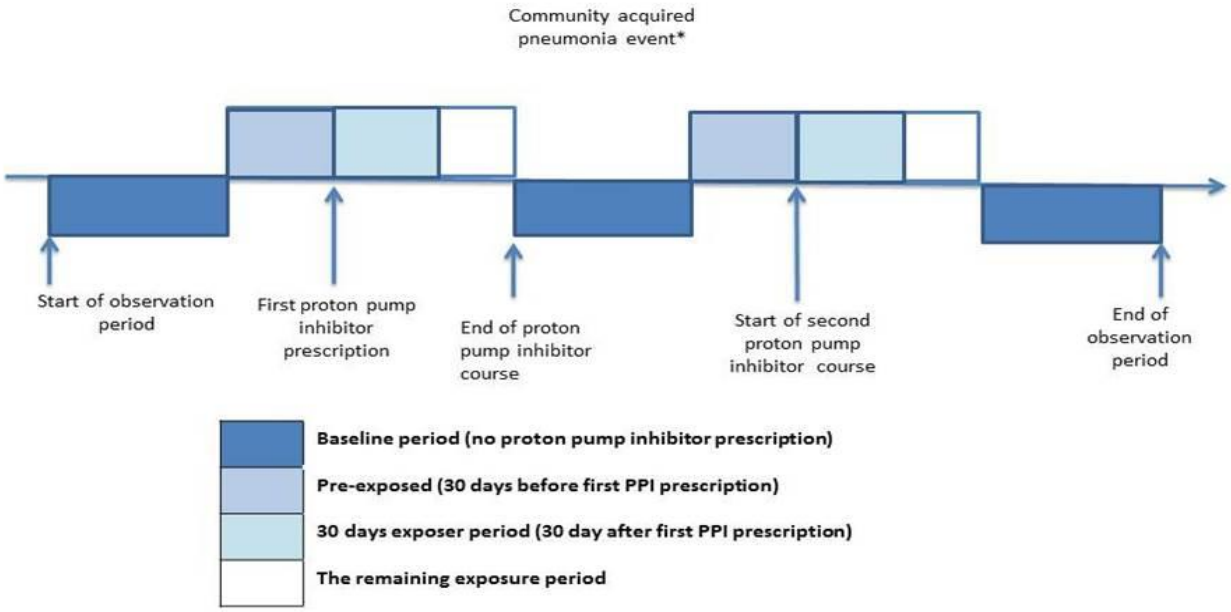

Figure 4-2 Illustration of self-controlled case series method showing division of time of each person included in this analysis to assess incidence of community-acquired pneumonia in relation to prescription for proton pump inhibitor. Events of pneumonia can occur during baseline or exposure period

4.3.3.2. Cohort study

- For this study design, the exposed patients were individually matched 1:1 by age (within five years), gender, and year of prescription with an unexposed cohort who had never received a PPI prescription. These unexposed controls were required also to have been contributing data for at least one year before their matched subject's first prescription. We included the following covariates in our study because they were identified as independent risk factors for pneumonia in previous studies(107,178), and because they have previously been associated with PPI use(179): smoking status (categorized into smoker, never smoked, or missing), alcohol use(categorized into never drink, ever drink, or missing), number of the visits to the GP in the year prior to the PPI prescription(below or equal to 5 visits or more than 5 visits), immunosuppression (defined as chemotherapy treatment within the last six months, systemic high-dose steroid treatment for 3 months, receipt of certain immunosuppressive medications, having a solid organ transplant with any anti-rejection medications within the previous year, or having diagnosis of human immunodeficiency virus infection(180)), and comorbidities which were

categorized based on the Charlson index score(142). This index is calculated using a list of conditions ,that comprised in the original score (in order of weighting), including :myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, leukaemia, lymphoma, moderate or severe liver disease, metastatic solid tumour, and acquired immunodeficiency syndrome(142,181). Previous work provides evidence that the Charlson comorbidity score is a valid predictor of mortality in linked primary and secondary care(181). Comorbidities were assessed using the entire patient record before the first PPI prescription date for the exposed cohort or the matched date for the unexposed cohort. Prescriptions of systemic corticosteroid and opioid (within 90 days before the prescription or matched date) were also included. In addition, we included data on the socioeconomic status measured using the Index of Multiple Deprivation (IMD) 2007. The information pertaining to these factors were extracted and evaluated from the CPRD primary care record both

for all CPRD patients and for the subset of patients with HES/ONS linked data.

4.3.4. Statistical analyses

Descriptive summary statistics were calculated for the study population by exposure status. We then performed the following analyses both for all CPRD patients and for the subset of patients with HES/ONS linked data. For each analysis we present results for our 3 different definitions of community-acquired pneumonia (broad primary care definition, narrow primary care definition, and hospital and mortality records based definition). We used the same cohort across the study designs to avoid using multiple cohorts because this may cause confusion when comparing the study results.

4.3.4.1. Self-controlled case series analysis:

Conditional Poisson regression models with fixed-effects(143,176) were used to calculate IRR comparing the incidence rate of community-acquired pneumonia during the exposure period with the incidence rate during the baseline period with adjustment for age (five-year bands). This allows the inclusion of multiple events of pneumonia during the observation period and adjusts for the correlations within individuals. The conditional Poisson regression model was used

in our analysis of recurrent events of community-acquired pneumonia for the following reasoning. Whilst the Poisson model assumes that the conditional variance equals the conditional mean, when the variance exceeds the mean (over-dispersion) an alternative method of Negative binomial regression should be used in the analysis(182). However a previous study showed that the fixed-effect Negative model leads to the same conditional estimator of the coefficient as the fixed-effect conditional Poisson model(182) as conditioning on the total count for each individual by using conditional Poisson regression removes the unobserved heterogeneity that is essential to the Negative binomial distribution. Furthermore, Armstrong et al, showed that conditional Poisson regression is good model to fit the over-dispersion and autocorrelation of panel data(183).

In this analysis, the data were expanded to panel data, so that each row corresponded to a single time interval for each case. We then identified the numbers of events that occurred within each interval. We excluded person-time following the pneumonia event until the day after the pneumonia resolution date because no additional events could occur for 84 days (an instance of immortal time) until the current pneumonia resolves.

4.3.4.2. Cohort study

Two analyses were performed using this study design: a multivariable Cox proportional hazards analysis and PERR.

4.3.4.2.1. Adjusted Cox regression analysis:

In this analysis we considered the first occurrence of community-acquired pneumonia after the index date. Cox proportional hazards modelling was used to estimate the HR for pneumonia in those receiving PPIs adjusted for potential confounders with 95%CI. The cohorts were followed from the date of their first PPI prescription until the earliest of the following: pneumonia event date, prescription end date, or study end date (this was considered as the earliest date of the following: end of observation time (1st August 2013), date of death, date transferred to a different practice, or last date of data collection from practice. The validity of the proportional hazards assumption was tested by plotting log-minus-log survival curves and carrying out Schoenfeld tests. Each potential confounder was included in the model only if it resulted in a 10% or greater change in the hazard ratio for pneumonia. Previous literature has found that this approach is superior to the alternative methods of selecting confounders

that have been applied in observational studies(184–186). Missing data were categorized into a separate category.

4.3.4.2.2. Prior event rate ratio (PERR):

The underlying assumption of the PERR analytical method in this study was that the comparison between pneumonia rate in exposed and unexposed patients before participating in the research should reflect the effect of the confounder (measured and non-measured) on pneumonia independent of the effect of the PPI therapy. PERR was estimated by the ratio of the unadjusted HR for community-acquired pneumonia during the year after initial PPI prescription of the exposed group versus the unexposed group, by the unadjusted HR for community-acquired pneumonia before one year of the PPI prescription of the exposed versus the unexposed. We set one year before and after PPI to limit the effect of unmeasured confounders that vary temporally in prior and post periods. The follow-up of patients in the year after initial PPI prescription ran from the date of their first PPI prescription until the earliest of, the anniversary of that date, the occurrence of a pneumonia event or the study end date. For the year prior to the initial PPI prescription, patients were followed from the date one-year before starting the PPI until the earliest of a pneumonia event, or the start of the PPI. We obtained the 95%CI of the PERR

by bootstrapping(144,145). Thus, patients were bootstrapped from the entire eligible CPRD source population to create a sample the same size as our cohort. We estimated the PERR adjusted HR for each bootstrap sample, repeated it 999 times, then sorted the PERR results and used the 2.5th and 97.5th as the lower and upper limits of the 95% confidence interval.

4.3.4.3. Sensitivity analyses

As with any statistical method, there are a number of assumptions that must be met for both the self-controlled case series analysis and PERR analysis methods to be considered reliable. We performed, therefore, the following sensitivity analyses to assess the possibility that these assumptions had been violated.

For the self-controlled case series: we performed a sensitivity analysis restricted to the first event of community-acquired pneumonia during the observation period to assess the assumption concerning the independence of recurrent outcome events. A second sensitivity analysis was conducted to assess the assumption that the occurrence of one event does not alter the probability of subsequent exposure. Although pneumonia is not a recognised indication, caution or contraindication to the use of PPIs, it is likely that

hospitalisation could lead to the administration of a PPI prescription(156). To account for this, we conducted an analysis that was limited to new users of PPIs who had not been hospitalised in the 60 days prior to the first PPI course. Finally, we performed a sensitivity analysis that excluded individuals who had died within 90 days of the recorded community-acquired pneumonia since it would only be possible for such cases to use PPIs prior to community-acquired pneumonia and not afterward.

For the PERR adjustment analysis: similar to the self-controlled case series analysis, we conducted an analysis that was limited to new users of PPIs who had not been hospitalised in the 60 days prior to the first PPI course to assess the assumption that the occurrence of one event does not alter the probability of subsequent exposure. Furthermore, we performed a sensitivity analysis restricted to non-fatal pneumonia on the basis that it would be impossible for fatal pneumonia cases to occur in the one year prior to the first PPI prescription, whilst it was possible for a fatal pneumonia to occur afterward. Also, we carried out a sensitivity analysis that was limited to cases before the point at which the first large population-based study suggesting an association was published in a specialised medical journal(104) , to minimise

the risk that the knowledge of patients' PPI use could affect diagnosis of pneumonia or previous pneumonia events affect the physician's decision to prescribe PPI.

For the Cox regression analysis and PERR, we performed a sensitivity analysis restricted to those over the age of 65 years (who are eligible to receive free prescription and therefore were less likely to purchase over the counter prescriptions), to the time period prior to the availability of the over counter PPIs in the UK(187).

4.3.4.4. Sample size calculation

We used the stpower Cox command to calculate the minimum number of events to detect a hazard ratio of 1.1 with 90% power and an alpha of 0.05. With an estimated incidence rate of 0.6 per 100 unexposed person years(95,104) we estimated that 160,000 patients were needed assuming an average 5 year follow up period for each patient and constant pneumonia risk over calendar time. This study population of 160,000 PPI exposed patients, therefore, was randomly sampled from the whole CPRD population according to the power calculation outlined above.

4.4. Results

We identified 160,000 new users of PPI during study period who were matched individually to an equal number of non-PPI exposed patients. The mean age at entry to the study was 56 years (standard deviation (SD) 16) for both exposed and unexposed cohorts and 55% of each cohort were females. Compared with unexposed patients, those prescribed PPIs were more likely to have a history of smoking (42.9% vs 33.7% of their matched controls) and alcohol use (29% vs 23.9%), they also had a higher burden of comorbidity, and used more corticosteroids and opioids (Table 4-1). HES-ONS linked information was available for 257,886 of the patients, whose characteristics were largely similar to those of the complete cohort (Table 4-2). The majority of the patients used PPI for a short period with median duration of 28 days(IQR 28 to 76 days).

Table 4-1 Demographic and clinical characteristics of the study population included in the cohort study by exposure status at cohort entry into the study period, for all CPRD patients

characteristic	Complete cohorts	
	Total number of patients 320,000	
	Unexposed N=160,000 (%)	Exposed N=160,000 (%)
smoking		
Never smoked	59,581 (37.2)	57,805 (36.1)
smoker	53,889 (33.6)	68,612 (42.8)
missing	46,530 (29.0)	33,583 (21.0)
Alcohol use		
Never drink	48,961 (30.6)	51,747 (32.3)
Ever drink	38,292 (23.9)	46,524 (29.0)
missing	72,747 (45.4)	61,729 (38.5)
Index of Multiple Deprivation (IMD) Quintiles*		
Unavailable	4,833 (3.0)	4,333 (2.7)
1(least deprived)	41,096 (25.7)	36,149 (22.5)
2	37,827 (23.6)	36,504 (22.8)
3	30,651 (19.2)	30,904 (19.3)
4	27,332 (17.1)	30,002 (18.8)
5(most deprived)	18,261 (11.4)	22,108 (13.8)
Charlson comorbidity index score		
0	99,492 (62.2)	72,290 (45.2)
1-2	48,287 (30.2)	63,461 (39.7)
3-4	9,510 (5.9)	17,494 (10.9)
>5	2,711 (1.7)	6,755 (4.2)
Number of GP visit		
Below 5 visits	87,286 (54.5)	37,605 (23.5)
Above 5 visits	72,714 (45.4)	122,395 (76.5)
Immunosuppression †	4,882 (3.0)	16,609 (10.3)
Non- topical Corticosteroid	5,832 (3.6)	15,990 (9.9)
Opioid prescriptions	1,557(0.9)	9,469(5.9)

CPRD=Clinical Practice Research Datalink.*Socioeconomic status is based on Index of multiple deprivation (IMD) and figures are the percentage of the people who had deprivation status available

†Immunosuppressed individuals defined according to the criteria to contraindicate vaccination(180)

Table 4-2 Demographic and clinical characteristics of the study population included in the cohort study by exposure status at cohort entry into the study period, for CPRD–HES subset patients.

characteristic	HES –ONS linked patients Total number of patients 257,886	
	Unexposed N=128,943 (%)	Exposed N=128,943 (%)
smoking		
Never smoked	47,243 (36.7)	45,757 (35.5)
smoker	43,633 (33.8)	55,935 (43.3)
missing	38,067 (29.5)	27,251 (21.1)
Alcohol use		
Never drink	40,394 (31.3)	42,716 (33.1)
Ever drink	29,364 (22.8)	36,246 (28.1)
missing	59,185 (45.9)	49,981 (38.8)
Index of Multiple Deprivation (IMD) Quintiles*		
Unavailable	24 (0.02)	26 (0.02)
1(least deprived)	34,359 (26.6)	29,987 (23.2)
2	31,588 (24.5)	30,236 (23.4)
3	25,464 (19.8)	25,739 (20.0)
4	22,542 (17.4)	24,867 (19.3)
5(most deprived)	14,966 (11.6)	18,088 (14.0)
Charlson comorbidity index score		
0	79,978 (62.0)	58,048 (45.0)
1-2	39,124 (30.3)	51,098 (39.6)
3-4	7,775 (6.0)	14,413 (11.2)
>5	2,066 (1.6)	5,384 (4.2)
Number of GP visit		
Below 5 visits	69,788 (54.1)	29,582 (22.9)
Above 5 visits	59,155 (45.8)	99,361 (77.0)
Immunosuppression †	3,866 (3.0)	13,723 (10.6)
Non- topical Corticosteroid	4,814 (3.7)	13,221 (10.2)
Opioid prescriptions	1,261 (0.9)	7,809 (6.0)

CPRD=Clinical Practice Research Datalink; Hospital Episode Statistics (HES) data and the Office for National Statistics (ONS) mortality data

*Socioeconomic status is based on Index of multiple deprivation (IMD) and figures are the percentage of the people who had deprivation status available

†Immunosuppressed individuals defined according to the criteria to contraindicate vaccination(180).

4.4.1. Cox regression analysis:

In this analysis, the exposed patients had an increased hazard of pneumonia defined by each of the 3 definitions of community-acquired pneumonia. Hazard ratios were greater when we more narrowly defined community-acquired pneumonia with unadjusted HRs of 5.44(95%CI 4.23 to 6.99) and 4.76 (95%CI 4.12 to 5.49) when we used narrow primary care definitions, and hospital and mortality records based definition, respectively (Table 4-3). In the adjusted analyses, the following potential confounders were found to have a substantial impact on the effect estimates for pneumonia: comorbidity index, number of GP visits, corticosteroid use, and immunosuppression. As such, they were included in the final model. After adjustment, the hazard of pneumonia by our broad primary care definition fell to 1.6 (95%CI 1.55 to 1.79) times that of controls in PPI exposed patients and the hazard ratios were similarly reduced by adjustment for confounding when our narrower primary care definitions of pneumonia were used (Table 4-3). In each case however there was a statistically significant excess of pneumonia in the exposed cohort. As the Charlson's index was developed to predict mortality and not morbidity, we carried out a separate analysis adjusted for individual comorbidities that resulted in a slight reduction in the HR (Table 4-3).

Table 4-3 Adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with proton pump inhibitors (PPI) according to the 3 different definitions of community-acquired pneumonia; Cox regression analysis.

	Pneumonia definition					
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**		**Hospital and mortality records based definition (in HES-ONS linked patients)**	
	320,000		**320,000**		**257,886**	
Parameter	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
Number of pneumonia event	1,582	3,798	74	392	234	1,090
Person years follow-up	52133	49885	52133	49885	43824	43456
Rate of pneumonia per 1,000 person years (95%CI)	30.34 (28.88 to 31.87)	76.13 (73.75 to 78.59)	1.37 (1.09 to 1.73)	7.31 (6.62 to 8.07)	5.48 (4.82 to 6.23)	25.74 (24.26to 27.32)
Unadjusted Hazard ratio (95%CI)	2.51 (2.36 to 2.67)		5.44 (4.23 to 6.99)		4.76 (4.12 to 5.49)	

Adjusted hazard ratio [a] (95%CI)	1.67 (1.55 to 1.79)	3.73 (2.69 to 5.16)	3.55 (3.03 to 4.16)
Adjusted hazard ratio [b] (95%CI)	1.65 (1.53 to 1.77)	3.87 (2.75 to 5.44)	3.54 (3.02 to 4.16)

HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

[a] Model adjusted for the confounders that changed the PPI hazard ratio by more than 10%: (comorbidity index, number of GP visits, corticosteroid use, and immunosuppression).

[B] Model adjusted for the potential confounding variables for pneumonia: (malignancy, cerebrovascular disease, hemiplegia, chronic pulmonary disease congestive, cardiac disease, lymphoproliferative disorders, dementia, diabetes, renal disease, rheumatological disease, myocardial infarction, and liver disease, in addition to number of GP visits, corticosteroid use, and immunosuppression

4.4.2. Self-controlled case series

From the exposed cohort, we identified 48,451 PPI exposed patients in CPRD with a record of at least one community-acquired pneumonia (broad primary care definition) with mean age of 60 years (SD 16 years), and 5,582patients in HES linked data who had a record of pneumonia related to hospital admission or death with mean age of 70 years (SD 14 years). Table 4-4 provides the IRRs for the different risk windows and pneumonia definition. Using our broad definition the IRR for pneumonia among PPI users was 1.19(95% CI 1.14 to 1.25) for 30 days after PPI prescription, and 1.49 (95% CI 1.46 to 1.52) for the remaining exposure period comparing to baseline period (Table 4-4). The IRR for the 30 before exposure was however even higher at 1.92 (95% CI 1.84 to 2.00). As for the Cox regression differences in ratios were higher for the more narrow definition of pneumonia (Table 4-4).

Table 4-4 Age adjusted incidence rate ratio and 95% confidence intervals for the association of community-acquired pneumonia(multiple events of pneumonia during the observation period)with proton pump inhibitors(PPI) according to the 3 different definitions of community-acquired pneumonia ;self-controlled case-series analysis

	Pneumonia definition								
	Broad primary care definition of pneumonia			**Narrow primary care definition of pneumonia**			**hospital and mortality records based definition (in HES-ONS linked patients)**		
Number of patients	**48,451**			**4,461**			**5,582**		
	No of events	PY	IRR(95%CI)	No of events	PY	IRR(95%CI)	No of events	PY	IRR(95%CI)
Baseline unexposed period	74,121	531201	1.0	3083	46254.4	1.0	7212	41172.2	1.0
Pre-exposed (30 days before first PPI prescription)	2,698	9099.32	1.92 (1.84 to 2.00)	212	798.275	3.72 (3.23 to 4.30)	642	815.828	4.16 (3.82 to 4.53)
30 days exposer period (30 day after first PPI prescription)	1,679	9067.54	1.19 (1.14 to 1.25)	151	791.452	2.70 (2.29 to 3.19)	393	802.223	2.69 (2.42 to 2.98)
The remaining exposure period	17,557	83720.3	1.49 (1.46 to1.52)	1,430	9262.69	3.18 (2.93 to 2.46)	3134	8824.76	2.44 (2.31 to 2.58)

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; IRR,I incidence rate ratio ;CI, confidence interval, PY, person years.

4.4.3. The PERR analysis:

The rate of pneumonia for the exposed patients was similar before a PPI prescription (62 per 1,000 person years of follow-up) to the rate after a PPI prescription (61.4 per 1,000 person years of follow-up), whilst the rate of pneumonia in unexposed patients increased over the study period (Table 4-5). The PERR for pneumonia (broad primary care definition) was 0.91(95%CI 0.83 to 0.99) based on an unadjusted post PPI hazard ratio of 2.06 (95% CI 1.98 to 2.14) divided by an unadjusted prior PPI hazard ratio of 2.26 (95% CI 2.18 to 2.35). Similarly, the PERR for pneumonia in the HES/ONS linked subset was 0.74 (95% CI 0.69 to 0.97) (Table 4-5).

Table 4-5 Unadjusted hazard ratio (95% confidence interval) for the association of community-acquired pneumonia with proton pump inhibitors(PPI) , before and after prescription, according to the 3 different definitions of community-acquired pneumonia ; Prior event rate ratio adjusted hazard ratio

	Pneumonia definition					
	Broad primary care definition of pneumonia		Narrow primary care definition of pneumonia		Hospital and mortality records based definition (in HES-ONS linked patients)	
Number of patients matched for date, gender and 5 years age band	**320,000**		**320,000**		**257,886**	
	Unexposed	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
BEFORE						
Pneumonia events (%)	4,298(2.6)	9,642(6.0)	178(0.1)	610(0.3)	553(0.4)	1,917(1.4)
Incidence of pneumonia per 1,000 per person years (95%CI)	27.24 (26.43 to 28.06)	62.07 (60.85 to 63.32)	1.11 (0.96 to 1.28)	3.81 (3.52 to 4.13)	4.29 (3.95 to 15.67)	14.94 (14.29 to15.62)
Hazard ratio(PPI/non-PP) (95%CI)	2.26 (2.18 to 2.35)		3.42 (2.89 to 4.04)		3.44 (3.12 to 3.78)	
AFTER						
Pneumonia events (%)	4,516(2.8)	8,727(5.45)	297 (0.1)	724 (0.4)	779(0.6)	1,684(1.3)
Incidence of pneumonia per 1,000 per person years (95%CI)	30.41 (29.54 to 31.31)	61.41 (60.14 to 62.71)	1.97 (1.76 to 2.20)	4.95 (4.60 to 5.33)	6.52 (6.08 to 7.00)	14.6 (13.92 to15.31)
Hazard ratio(PPI/non-PP) (95%CI)	2.06 (1.98 to 2.14)		2.82 (2.44 to 2.36)		2.55 (2.33 to 2.80)	
Prior event rate ratio(PERR)* (95%CI)	**0.91 (0.83 to 0.99)**		**0.82 (0.53 to 1.20)**		**0.74 (0.69 to 0.97)**	

PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

4.4.4. Sensitivity analysis:

For the self-controlled case series analysis, restricting the primary analysis to only the first event recorded resulted in reductions in the observed rate ratios of pneumonia following PPI prescriptions while there was no change in the risk of pneumonia prior to the PPI prescription (Table 4-6). The results of the analysis aiming to assess whether prior hospitalisation could influence the likelihood of PPI initiations revealed that around 8,756 patients (20%) who were included in the self-controlled case series analysis had been hospitalised prior to the first PPI prescription. Of those, around 13% had been hospitalised for community-acquired pneumonia. After excluding those patients, the IRR for community-acquired pneumonia (using our broad primary care definition of pneumonia) was very similar to that from our primary analysis and our conclusion remained that the risk of pneumonia predates PPI prescription (Table 4-7). Around 5% died within 90 days of the date of pneumonia diagnosis and the results of the analysis excluding these patients showed a reduction in the IRR for pneumonia for 30 days after PPI prescription and for the remaining exposure period (Table 4-8).

For the PERR method, 25,733 (10%) of patients had previously been hospitalised within the 60 days before the first PPI prescription. Of those, 8% were hospitalised for pneumonia. Repeating the PERR analysis after excluding those patients did not appreciably alter the result of the primary PERR analysis (Table 4-9). Similarly, the analysis to test for a possible violation of the underlying assumption concerning the effect of mortality produced similar results to the primary analysis as the percentage of mortality was low among the cohort included in the PERR analysis (Table 4-10).

The results from the remaining sensitivity analyses were very similar to those from the whole population for Cox regression, and PERR analyses (Table 4-11,Table 4-12,Table 4-13,Table 4-14, and Table 4-15).

Table 4-6 Sensitivity analysis: self-controlled case-series analysis restricted to the first event of pneumonia during the observation period. (Age adjusted incidence rate ratio and 95% confidence intervals).

Period	Pneumonia definition Broad primary care definition of pneumonia (n=48,451)			Narrow primary care definition of pneumonia (n=4,461)			Hospital and mortality records based definition (in HES-ONS linked patients) (n=5,582)		
	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)
Baseline unexposed period	40,236	550492	1.0	2880	46780	1.0	3840	43714.2	1.0
Pre-exposed (30 days before first PPI prescription)	1257	9550.72	1.70 (1.60 to 1.80)	199	825.79	3.69 (3.18 to 4.28)	323	886.324	3.71 (3.30 to 4.17)
30 days exposer period (30 day after first PPI prescription)	722	9514.02	0.98 (0.91 to 1.05)	132	822.65	2.46 (2.06 to 2.94)	222	881.281	2.57 (2.24 to 2.95)
The remaining exposure period	6236	88291.2	1.00 (0.97 to 1.04)	1250	9467.2	2.98 (2.73 to 3.26)	1197	9264.62	1.62 (1.49 to 1.75)

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
HES=Hospital Episode Statistics; IRR=incidence rate ratio; ONS=Office for National Statistics

Table 4-7 Sensitivity analysis: self-controlled case-series analysis after excluding cases with previous hospitalization.(Age adjusted incidence rate ratio and 95% confidence intervals).

	Pneumonia definition					
	Broad primary care definition of pneumonia			Narrow primary care definition of pneumonia		
Period	**(n=34,122)**			**(n=2,682)**		
	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)
Baseline unexposed period	44,943	319090	1.0	1,734	23956.3	1.0
Pre-exposed (30 days before first PPI prescription)	1,722	6034.81	1.85 (1.76 to 1.94)	73	470.322	1.96 (1.54 to 2.49)
30 days exposer period (30 day after first PPI prescription)	1,066	5998.49	1.15 (1.08 to 1.22)	73	467.762	1.98 (1.56 to 2.52)
The remaining exposure period	9,101	45147.2	1.42 (1.38 to 1.47)	641	4362.37	2.57 (2.28 to 2.91)

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
IRR, incidence rate ratio ;CI, confidence interval

Table 4-8 Sensitivity analysis: self-controlled case-series analysis excluding patients who died within 90 days of the date of pneumonia diagnosis. (Age adjusted incidence rate ratio and 95% confidence intervals)

	Pneumonia definition								
	Broad primary care definition of pneumonia			Narrow primary care definition of pneumonia			hospital and mortality records based definition (in HES-ONS linked patients)		
Period	(n=46,496)			(n=3,554)			(n=3,870)		
	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)
Baseline unexposed period	71,348	515040	1.0	2,633	38370.3	1.0	4,485	30278.6	1.0
Pre-exposed (30 days before first PPI prescription)	2,539	8827.25	1.86 (1.79 to 1.94)	194	661.005	3.96 (3.40 to 4.60)	350	612.526	3.57 (3.19 to 4.00)
30 days exposer period (30 day after first PPI prescription)	1,490	8803.66	1.09 (1.04 to 1.15)	102	656.287	2.11 (1.72 to 2.58)	224	606.556	2.32 (2.02 to 2.66)
The remaining exposure period	16,023	80970.8	1.39 (1.35 to 1.42)	936	7809.01	2.05 (1.86 to 2.26)	1,561	6735.69	1.71 (1.59 to 1.84)

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
HES=Hospital Episode Statistics; IRR=incidence rate ratio; ONS=Office for National Statistics

Table 4-9 : Sensitivity analysis: PERR analysis after excluding cases with previous hospitalization, according to the 2 different definitions of community-acquired pneumonia

	Pneumonia definition			
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**	
Parameter	**265,650**		**265,650**	
	unexposed	**Exposed**	**unexposed**	**exposed**
Before prescription				
Pneumonia events	3,353(2.5)	7,300(5.5)	126(0.1)	321(0.2)
Incidence of pneumonia per 1,000 per person years (95%CI)	25.57 (24.72 to 26.45)	56.49 (55.21 to 57.80)	1.10 (0.79 to 1.13)	2.41 (2.16 to 2.69)
Hazard ratio(PPI/non-PP) (95%CI)	2.20 (2.11 to 2.29)		2.54 (2.07 to 3.13)	
After prescription				
Pneumonia events	3,518(2.6)	6,603(4.9)	222 (0.1)	428 (0.3)
Incidence of pneumonia per 1,000 per person years (95%CI)	26.86 (25.99 to 27.76)	51.09 (49.87 to 52.34)	1.78 (1.56 to 2.03)	3.50 (3.18 to 3.85)
Hazard ratio(PPI/non-PP) (95%CI)	1.91 (1.82 to 1.98)		2.15 (1.82 to 2.55)	
Prior event rate ratio(PERR)*	**0.86 (0.74-0.97)**		**0.84 (0.65-1.16)**	

PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. CI, confidence interval

Table 4-10 Sensitivity analysis: PERR analysis after excluding patients who died within 90 days of the date of pneumonia diagnosis, according to the 3 different definitions of community-acquired pneumonia

	Pneumonia definition					
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**		**Hospital and mortality records based definition (in HES-ONS linked patients)**	
	249,816		**249,860**		**195,770**	
Parameter	**unexposed**	**exposed**	**unexposed**	**exposed**	**Unexposed**	**exposed**
Before prescription						
Pneumonia events	3,217(2.5)	7,190(5.7)	132(0.1)	396(0.3)	327(0.3)	1,070(1.09)
Incidence of pneumonia per 1,000 per person years (95%CI)	26.10 (25.21 to 27.02)	59.23 (57.88 to 60.62)	1.05 (0.89 to 1.25)	3.17 (2.87 to 3.50)	3.34 (3.00 to 3.72)	10.97 (10.33 to 11.65)
Hazard ratio(PPI/non-PP) (95%CI)	2.26 (2.17 to 2.36)		3.00 (2.46 to 3.65)		3.25 (2.87 to 3.68)	
After prescription						
Pneumonia events	3,461(2.7)	6,870(5.5)	141 (0.1)	343 (0.2)	362(0.3)	910(0.9)
Incidence of pneumonia per 1,000 per person years (95%CI)	28.11 (27.18 to 29.06)	56.63 (55.30 to 57.98)	1.12 (0.95 to 1.33)	2.74 (2.46 to 3.05)	3.70 (3.34 to 4.10)	9.34 (8.75 to 9.96)
Hazard ratio(PPI/non-PP) (95%CI)	2.01 (1.93 to 2.10)		2.45 (2.01 to 2.98)		2.54 (2.25 to 2.88)	
Prior event rate ratio(PERR)*	**0.88 (0.79 to 0.97)**		**0.81 (0.62 to 1.00)**		**0.78 (0.60 to 1.01)**	

PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Table 4-11: Sensitivity analysis: PERR analysis restricted to those over the age of 65 years, according to the 3 different definitions of community-acquired pneumonia.

	Pneumonia definition					
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**		**hospital and mortality records based definition (in HES-ONS linked patients)**	
Parameter	**99,294**		**99,294**		**81,556**	
Before prescription						
Pneumonia events	2,003 (4.03)	4,082 (8.22)	89(0.20)	358 (0.72)	116(0.28)	442(1.08)
Incidence of pneumonia per 1,000 per person years (95%CI)	41.22 (39.46-43.07)	85.57 (82.99-88.24)	1.97 (1.62-2.40)	7.22 (6.51-8.01)	2.84 (2.37-3.41)	10.87 (9.90-11.93)
Hazard ratio(PPI/non-PP) (95%CI)	2.07 (1.98-2.19)		3.66 (2.92-4.57)		3.82 (3.11-4.69)	
After prescription						
Pneumonia events	2,204 (4.44)	3,816 (7.69)	212 (0.43)	482 (0.97)	267 (0.65)	678 (1.66)
Incidence of pneumonia per 1,000 per person years (95%CI)	48.05 (46.09 - 50.10)	90.98 (88.14 - 93.9)	4.52 (3.95 - 5.17)	11.06 (10.12 - 12.10)	7.04 (6.24 - 7.93)	19.31 (17.91 -20.82)
Hazard ratio(PPI/non-PP) (95%CI)	1.88 (1.78 to 1.98)		2.43 (2.07 to 2.86)		2.72 (2.36 to 3.14)	
Prior event rate ratio(PERR)*	**0.90 (0.83 to 1.01)**		**0.66 (0.46 to 1.60)**		**0.71 (0.3 to 1.11)**	

PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Table 4-12: Sensitivity analysis: PERR analysis restricted to the time period prior to the availability of OTC PPIs, according to the 3 different definitions of community-acquired pneumonia.

	Pneumonia definition					
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**		**hospital and mortality records based definition (in HES-ONS linked patients)**	
	45,146		**45,146**		**27,704**	
Parameter	**unexposed**	**exposed**	**unexposed**	**exposed**	**unexposed**	**exposed**
Before prescription						
Pneumonia events	721(3.1)	1,366(6.0)	33(0.1)	87(0.3)	70(0.5)	293(2.1)
Incidence of pneumonia per 1,000 per person years (95%CI)	28.32 (26.19 to 30.62)	66.17 (62.85 to 69.67)	1.46 (1.04 to 2.05)	3.86 (3.12 to 4.76)	5.06 (4.00 to 6.40)	21.31 (19.00 to 23.89)
Hazard ratio(PPI/non-PP) (95%CI)	2.34 (2.13-2.58)		2.63 (1.76-3.93)		4.12 (3.17 to 5.36)	
After prescription						
Pneumonia events	721 (3.19)	1,366 (6.05)	62 (0.27)	119 (0.53)	124 (0.9)	238 (1.7)
Incidence of pneumonia per 1,000 per person years (95%CI)	33.23 (30.89 to 35.75)	65.89 (62.49 to 69.48)	2.81 (2.19 to 3.60)	5.56 (4.65 to 6.66)	9.20 (7.72 to 10.97)	18.37 (16.18 to 20.86)
Hazard ratio(PPI/non-PP) (95%CI)	2.02 (1.84 to 2.22)		2.53 (1.80 to 3.54)		2.09 (1.66 to 2.62)	
Prior event rate ratio(PERR)*	0.86 (0.77 to 0.95)		0.96 (0.75 to 1.17)		0.50 (0.44 to 0.82)	

PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Table 4-13 Sensitivity analysis: PERR analysis restricted to cases before the first large population-based study was published according to the 3 different definitions of community-acquired pneumonia.

	Pneumonia definition					
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**		**hospital and mortality records based definition (in HES-ONS linked patients)**	
	77,972		**77,972**		**57,982**	
Parameter	**unexposed**	**exposed**	**unexposed**	**exposed**	**unexposed**	**exposed**
Before prescription						
Pneumonia events	1,034(2.6)	2,465(6.3)	57(0.1)	166(0.4)	171(0.5)	649(2.2)
Incidence of pneumonia per 1,000 per person years (95%CI)	26.88 (25.29 to 28.57)	65.27 (62.74 to 67.90)	1.46 (1.12 to 1.89)	4.26 (3.66 to 4.96)	5.91 (5.09 to 6.87)	22.57 (20.89 to24.37)
Hazard ratio(PPI/non-PP) (95%CI)	2.43 (2.26 to 2.62)		2.91 (2.15-3.93)		3.78 (3.19 to 4.47)	
After prescription						
Pneumonia events	1,208(3.1)	2,383(6.1)	97(0.27)	211 (0.54)	253 (0.8)	503 (1.7)
Incidence of pneumonia per 1,000 per person years (95%CI)	32.28 (30.51 to 26.45)	66.84 (64.21 to 69.58)	2.55 (2.09 to 3.11)	5.74 (5.01 to 6.56)	8.99 (7.95 to 10.17)	18.59 (17.03 to20.29)
Hazard ratio(PPI/non-PP) (95%CI)	2.13 (1.98 to 2.29)		2.68 (2.06 to 3.49)		2.25 (1.92 to 2.64)	
Prior event rate ratio(PERR)*	0.87 (0.86 to 0.98)		0.92 (0.59 to 1.13)		0.59 (0.48 to 0.95)	

*PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Table 4-14 Sensitivity analysis: adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with proton pump inhibitors (PPI) according to the 3 different definitions of community-acquired pneumonia; restricted to those over the age of 65 years.

	Pneumonia definition					
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**		**hospital and mortality records based definition (in HES-ONS linked patients)**	
Parameter	**99,294**		**99,294**		**80,974**	
	unexposed	**exposed**	**unexposed**	**exposed**	**unexposed**	**exposed**
Number of pneumonia events	902(1.8)	2,047(4.1)	53(0.1)	281(0.5)	212(0.52)	885(2.1)
Rate of pneumonia per 1,000 person years(95%CI)	21.63 (39.05 to 44.49)	99.25 (95.04 to 103.64)	2.35 (1.79 to 3.08)	12.50 (11.12 to 14.05)	11.70 (10.23 to 13.39)	49.59 (46.43 to 52.97)
Unadjusted Hazard ratio (95%CI)	2.35 (2.16 to 2.54)		5.50 (4.08 to 7.42)		4.27 (3.67 to 4.97)	
Adjusted hazard [a] (95%CI)	1.61 (1.47 to 1.77)		4.02 (2.78 to 5.82)		3.27 (2.77 to 3.86)	

HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval
[a] Adjusted model for the confounders that changed the multivariate Cox model by more than 10%: comorbidity index, number of GP visits, corticosteroid use, and immunosuppression

Table 4-15 Sensitivity analysis: adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with proton pump inhibitors (PPI) according to the 3 different definitions of community-acquired pneumonia; restricted to the time period prior to the availability of OTC PPIs.

	Pneumonia definition					
	Broad primary care definition of pneumonia		**Narrow primary care definition of pneumonia**		**hospital and mortality records based definition (in HES-ONS linked patients)**	
	45,146		**45,146**		**27,704**	
Parameter	**unexposed**	**exposed**	**unexposed**	**exposed**	**unexposed**	**exposed**
Number of pneumonia events	280	640	12(0.1)	71(0.3)	39(0.2)	140(1.0)
Rate of pneumonia per 1,000 person years (95%CI)	31.06 (27.62to 34.92)	75.23 (69.62 to 81-29)	1.28 (0.72 to 2.26)	7.61 (6.03 to 9.61)	6.68 (4.88 to 9.15)	24.22 (20.52 to 28.58)
Unadjusted Hazard ratio (95%CI)	2.41 (2.08 to 2.79)		5.91 (3.20 to 10.90)		3.63 (2.53 to 5.20)	
Adjusted hazard a (95%CI)	1.39 (1.16 to 1.67)		4.72 (1.66 to 13.39)		3.26 (2.13 to 5.01)	

CI, confidence interval

[a] Adjusted model for the confounders that changed the multivariate Cox model by more than 10%: comorbidity index, number of GP visits, corticosteroid use, and immunosuppression.

4.5. Discussion

4.5.1. Summary of the result:

This study has shown that there is a crude association between PPI prescriptions and an increased rate of community-acquired pneumonia, but that this is explained by an underlying increased pneumonia risk in patients preceding a PPI prescription. Furthermore after adjusting for confounding and changes over time the relative rate of community-acquired pneumonia actually fell following PPI prescriptions.

4.5.2. Strengths and limitations:

4.5.2.1. Limitations and strengths of the data used in this study

A major strength of this study is that we have used routinely collected general practice records to conduct it. This provides for an unbiased selection of both the exposed and control cohorts and reduces the opportunity for information bias (since both PPI prescription and pneumonia diagnosis were prospectively collected independently). In addition since the base population is representative of the UK general population, our results are likely to be generalisable at least to the UK population and to other similar populations(129). However,

the generalisability of self-controlled case series analysis is limited as patients who are included may have a different underlying risk for community acquired pneumonia than the baseline population.

A further strength is that data were available relating to a number of potential confounders allowing us to control for the effects of these in the Cox regression models. Although there is evidence(131) to suggest that recording lifestyle risk factors in CPRD, such as smoking and alcohol use, has improved in the UK primary care setting, missing data is unavoidable and increases the risk of residual confounding by these factors in addition to unmeasured confounding. In this study, there was a considerable amount of missing data pertaining to patients' alcohol and smoking habits, and we allowed for this by incorporating the use of an indicator variable for missingness. The use of a more modern approach, such as multiple imputation, could be viable. However, adjusting for the effects of smoking status, in which the missing data was dealt with as a separate category in the statistical model, did not change the HR; as such, it was not included as a confounder in the model. Previous studies have demonstrated that, in situations in which data pertaining to smoking status is missing, the individuals involved tend to be more likely to be ex-smokers or non-smokers than smokers(139). Therefore, I believe that

dealing with missing data as a separate category represented an acceptable approach to avoiding the further complication of the many analyses presented in this study. In addition, in this study, I used two analytical methods to specifically address the effect of confounders that were difficult to measure or incompletely measured.

One potential limitation is the possibility of error in our assessment of exposure since CPRD data only includes information about the prescriptions and does not prove that the prescribed drug has been taken. In this study we assumed that patients did fill their prescriptions on the same day as they were issued, and that the patients took their medication as prescribed. This assumption could lead to a misclassification of exposure status, especially in the case of patients who took PPI intermittently. However, as PPIs are initially prescribed for symptom control, this may not lead to a large overestimation. Additionally, previous studies reported that relying on prescription information as a surrogate for its use are unlikely to introduce significant misclassification(107).

Also, the CPRD data do not include information on proportion of PPI users who obtain their prescription OTC which could lead to underestimation of PPI use among the exposed.

However, Omeprazole became available for purchase OTC from community pharmacies from 2002 in UK (187) and prescribed PPI use continued to rise since ,so it is unlikely that this has led to a large underestimation. Additionally, we assessed this by two sensitivity analyses: the first was restricted to those over the age of 65 years who received free prescriptions and were therefore are less likely to purchase over the counter prescriptions. The second was restricted to the time period prior to the availability of OTC PPIs. And the results from these sensitivity analyses were very similar to those from the whole population for Cox regression and PERR analyses.

4.5.2.2. Limitations and strengths of the analytic methods

There are in addition some potential limitations and strengths directly related to the analytical techniques we have chosen. Firstly, for the cohort study design start time bias may affect this analysis where outcomes have a varying incidence over time in the background population. We choose start times for unexposed subjects that are identical to their matched exposed subjects to eliminate this bias. The imbalance observed in the measured covariates between exposed and unexposed patients, therefore, is likely because patients who

were prescribed PPI have other comorbid conditions. This also has been reported in previous studies(107,115) and may explain the higher baseline rate of pneumonia in patients who received PPI prescription.

Second, we used the same patients as their own control in the case series method to minimise confounding owing to patients' characteristics and comorbidities. The conditional Poisson regression model represented an effective choice in our analysis of recurrent events of community-acquired pneumonia because previous studies (182,183) have proven it to be effective in terms of the over-dispersion and autocorrelation of panel data. we have further assessed this by applying an assessment, that was suggested by Armstrong et al(183), that adjusts the estimates for over-dispersion after using conditional Poisson regression command (xtpossion). Applying this assessment to our analysis yielded similar result to our primary analysis, suggesting that conditional Poisson regression with fixed effect was a reasonable choice for the self-controlled case series analysis.

Also, we examined the key assumptions underlying the self-controlled case series method by looking for evidence that the occurrence of pneumonia does not alter the risk of subsequent

PPI prescription. Excluding those patients who had been hospitalized or died following pneumonia events from the main analyses had no substantial effect on the results. However, as this method adjusts for a fixed relative difference in confounders between the exposed and unexposed, it does not reduce confounding due to factors that may vary over time differently between the exposed and unexposed.

We also attempted to overcome the limitations of prior observational work by utilising a newer analytic technique, PERR, which has been proposed as a method of controlling for unmeasured time-fixed confounding(144,145). PERR was able to adjust both for the underlying increased risk of pneumonia in patients who were prescribed PPIs (that confounded a standard Cox regression), and for changes in pneumonia incidence over time (that may have confounded the case series analysis). Although PERR methods offer a promising approach to address biases that can arise in observational studies, in practice we cannot exclude all situations where prior events might influence future treatments. A recent study tried to minimize the bias that could result from using PERR by deriving a flexible pairwise Cox likelihood function to PERR_ALT approach(172). They showed that the PERR-ALT method is consistent under relevant assumptions; however,

they also confirmed that all models(PERR ,PERR-ALT, and Cox model) are biased if any interaction between treatment and unmeasured confounders takes place or the confounder changes over time.

In our study we attempted to carefully assess the potential biases by examining the possible causes of violations of the PERR assumptions via either hospitalisations, death or the publication of studies of pneumonia risks influencing PPI prescriptions, and found no evidence to suggest that PERR represented an inappropriate analytic technique in our study.

4.5.3. Comparison with existing literature

Numerous studies have examined the association between PPI therapy and the risk of community-acquired pneumonia. Early observational studies showed that using PPI therapy might be associated with an increased risk of community-acquired pneumonia (104,105,108). Further studies suggested that a dose response relationship supported the causality association(104,109), whilst yet others argued that any temporarily increased risk suggested the presence of protopathic bias (115,116).There have also been studies including a retrospective analysis of the original safety data from several randomised clinical trials of esomeprazole(one

specific PPI)(106), failing to show any such an association despite statistical adjustment for confounders(107,111). Concern however was amplified by findings from meta-analyses based on these observational studies that showed that the risk of community-acquired pneumonia was 34%(96) and 49%(113) higher among patients that use PPIs than it was among nonusers, with a temporal relation soon after initiation of the PPI therapy. Thus, evidence linking PPI therapy to the risk of community-acquired pneumonia remains inconclusive.

We have examined the association of PPI use and community-acquired pneumonia and assessed whether residual and time-fixed confounding explains this association. The results of the adjusted Cox regression model in this study did not differ from those of previous studies that used CPRD data and found similar association. However, self-controlled case series analysis shows that this risk predates prescription and the PERR analysis suggests the significant association observed can be attributed to confounding. Previous studies have reported that the highest risk of pneumonia occurs in the first 30 days, while we observed an IRR of 1.19 in the 30 days after PPI prescription and 1.49 for the remaining exposure period. This apparent contradiction may be explained by

differences in the subpopulations of patients taking long-term and short-term PPI since most courses in our data were short term, the initial 30 days will primarily reflect these patients whereas the later period will be long term users.

Our findings from the PERR analysis are comparable to a recent study that analysed the pooled adverse event data related to respiratory tract infection reported in randomized double-blind clinical studies that were specific to esomeprazole(188). The reported relative risk for pneumonia in patients receiving esomeprazole compared to the placebo in that study was 0.66(95%CI 0.36-1.22)(188). Though the populations recruited to RCTs are often not typical of those receiving PPIs in general practice, our results suggest that these findings may well be widely generalisable. This comparison is also we think an important validation of the PERR methodology which has had limited use previously.

In our PERR analysis, a modest protective effect was associated with PPI use and our narrower definitions of pneumonia. Although we don't have a compelling explanation for our findings, it is possible that PPI use protects against severe acid reflux in those patients who are suffering from severe GORD and, in our narrower definitions of pneumonia,

the accurate cases of severe pneumonia have been identified than the broader definition leading to the appearance of the protective or null effect of PPI therapy in the analysis of more severely defined outcomes. These results were similar to the effect estimates that have been reported in the previous retrospective analysis of data related to esomeprazole(106,188). Therefore, this would not alter the interpretation of our conclusion.

4.6. Conclusion

Our results indicate that there is no strong evidence to support the association between the use of PPIs and an increase in the risk of community-acquired pneumonia. Patients who are prescribed PPIs have an underlying risk of community-acquired pneumonia before receiving the PPI prescription. Therefore, it is likely that patient characteristics, comorbidity, and severity of gastroesophageal reflex disease (115,116), were the main contributors to the increased risk of pneumonia observed in patients who were prescribed PPI.

Chapter Five

The Risk of Clostridium Difficile Infection and Of Community-Acquired Pneumonia in Patients with Pernicious Anaemia: A Retrospective Cohort Study Using Primary Care Database.

5.1. Introduction

This chapter examines whether a reduction in gastric acidity is the underlying mechanism of the increased risk of infection (community-acquired pneumonia or C. difficile infection) in patients who use PPI therapy through examining the risks of these infections occurring in patients who have pernicious anaemia with presumed chronic achlorhydria. The unadjusted and adjusted HR showing the risk of developing pneumonia and C. difficile infection in patients with pernicious anaemia compared to the controls are presented followed by a discussion of these findings and their implications.

This study was approved by the ISAC (protocol number 15_240R). Part of the findings presented in this chapter has been published in a peer-reviewed journal(189).

5.2. Background

Although the existing studies that have reported an association between the use of PPI and community-acquired pneumonia or C. difficile infection have postulated that PPI-associated hypochlorhydria explain the observed increased risk of infections(96,99,113,124,125), this has not been conclusively proven since there are alternative and viable explanations. For example, there is a possibility that the relationship between PPI use and the risk of infection is

confounded by patient's characteristics and the severity of comorbidities in the case of community-acquired pneumonia(115). In the case of C. difficile infection, some studies have indicated that C. difficile spores, which are the major mode of transmission, are acid resistant(99), adding to the emerging evidence that suggests that factors within patients who are prescribed PPI are responsible for the increased risk of gastrointestinal infection in those patients(118). An important comparable group of patients with persistent reduction in stomach acidity are pernicious anaemia patients.

Pernicious anaemia is an autoimmune condition in which there is atrophy of gastric mucosa as a result of autoantibodies directed against the parietal cell, which lead to subsequent achlorhydria, failure of intrinsic factor production and subsequent vitamin B12 malabsorption(1,190). Since some studies have hypothesised that the increase in gastric pH facilities bacterial colonisation in the stomach leading to increased risk of pneumonia or influence the risk of C. difficile infection(97–99), patients with pernicious anaemia should also have an increased risk of these infections. We have, therefore, conducted a study that primarily aimed to assess whether pernicious anaemia patients are at an increased risk of

developing community-acquired pneumonia or C. difficile infection. Demonstrating this association would help to bridge the gap in understating with regards to the casual mechanisms at play in the relationship between the use of PPI and these infections. If there is an increased risk of infections in patients with pernicious anaemia, this would act as further evidence that the hypochlorhydria induced by PPI therapy could directly cause the increased risk of pneumonia or C. difficile infection in patients who receive them. On the contrary, if there is no or a moderate association, this would suggest that the observed association between PPI and infection may have some other cause.

5.3. Methods

5.3.1. Study design:

We performed a matched cohort study.

5.3.2. Study population:

We used our source population i.e. all adult individuals with an acceptable registration status within the CPRD from 1990 to 2013 who had at least one year of active registration following the date of current registration or the date the practice became UTS on CPRD, whichever was the latest, to select the study population for this cohort study. We identified within these a subgroup of patients for whom linked HES data was

available to increase the sensitivity of detecting outcomes by including hospital data. Within this subgroup we used both CPRD and HES data to define the cases and outcome events where the first diagnosis recorded in either data source was selected as the event date. For this subset, the follow-up period was also modified to ensure it was consistent with the linkage coverage period from 1997 to 2012.

5.3.3. Identification of exposed and unexposed cohort

From the list of eligible patients, we selected adult patients who had a coded diagnosis of vitamin B12 deficiency anaemia or pernicious anaemia(Appendix 3) and who had been prescribed concurrent vitamin B12 therapy(BNF section,9.1.2 (31)), the current standard of care for this condition. We excluded patients from the exposed cohort who were receiving vitamin B12 therapy, but had a pre-existing alternative aetiology, such as gastrectomy, intestinal resection, generalised malabsorption, or PPI use. PPI use was considered to be the indication if the date of the B12 prescriptions fell within the period of continuous use of PPI prior to cohort entry. The start of follow-up for the exposed group was the date of diagnosis or the first date of UTS prospective data if the UTS date was later than the date of diagnosis.

Ten unexposed patients for each case were randomly matched for age (within five years), gender, general practice, and the start date of follow-up with a matched exposed patient. All patients that met the inclusion criteria for the exposed cohort group, and all those who were receiving vitamin B12 prescriptions for indications other than pernicious anaemia, were excluded from the control group.

The end of the follow-up was defined as the earliest date of the following: date of the first outcome event on record, end of observation time (1st August 2013), date of death, date transferred to a different practice, or the last download from their practice. Patients were censored if they developed one of the alternative aetiologies after commencing vitamin B12 therapy. If the patient was issued a PPI prescription after cohort entry, they were censored on the date of the PPI prescription.

5.3.4. Outcome and covariates

Community-acquired pneumonia and C. difficile infection were the primary outcomes in this study. We used our broad primary care definition of community-acquired pneumonia (Appendix 2). Outcomes for C. difficile infection were identified by the occurrence of C. difficile infection based on the clinical diagnosis recorded and/or positive C. difficile toxin assay

(Appendix 4). We used information from both primary care and HES data in the subgroup of patients with available linked data, to additional outcomes with an ICD-10 code (ICD code A04.7 for Clostridium Difficile colitis and Appendix 5 for pneumonia). The first diagnosis recorded in either data source was considered to represent the event date.

Many possible confounders were identified in this study that were associated with pernicious anaemia and recognised as independent risk factors for community-acquired pneumonia(178) and/or C. difficile infection(191). We examined the following potential confounding patient characteristics and medical conditions: socioeconomic status (using individual IMD quintiles), co morbidity as measured by the Charlson index(142), smoking(categorized into smoker, never smoked, or missing), hospitalisation, and the use of acid-suppressing medication, immunosuppressant drugs, antibiotics, and corticosteroids. As it is likely that any missing data was non-random particularly for smoking, we modelled missingness as a separate category.

5.3.5. Statistical analyses

Descriptive analyses were carried out to compare the baseline characteristics between case and control groups. We used a two-sided likelihood ratio chi-square test for categorical

variables. We carried out a multivariable Cox regression analysis to assess the impact of independent variables on the outcome (first failure) in each study across the time. We checked for violation of the proportional hazards assumption in these models via log-log plots and Stata's estat phtest command. Variables significantly associated with outcome in the univariate analysis were entered in the regression models if they were significantly associated with the outcome in univariate analysis ($P \leq 0.05$), and retained in the final model if their inclusion altered the apparent effect size of the univariate Cox model by at least 10%. Observational studies have found this approach to be superior to other methods of selecting confounders(186).

We considered drug exposure variables as time-varying covariates (use of acid suppressing medication, immunosuppressant drugs, antibiotics, and corticosteroids). Thus, the follow-up time for each patient was first split into year-long blocks of time, then the drug exposure status was determined for each yearly block. Medical comorbidities were measured at baseline, and categorised using the Charlson index derived from primary care data (181). Given that the two main clinical manifestations of pernicious anaemia are vitamin B12 deficiency and achlorhydria, adjusting for the use of PPI or acid-suppression medication was considered to be a

potential confounder in the study analysis because these medications also suppress the production of gastric acid, which may lead to the malabsorption of vitamin B12 medications. As both the use of antibiotics(192) and hospitalization(191) are risk factors for C. difficile infection, we include these two as potential confounding factors for the association between pernicious anaemia and risk of C. difficile infection where both of them were considered as time varying covariates.

5.3.6. Sensitivity analyses

For both outcomes, we carried out two sensitivity analyses. First, to ensure that the results were not altered by any survival bias in cases, we restricted the analysis to the subgroup of patients who were diagnosed with pernicious anaemia for the first time with at least one year of follow-up in CPRD within the study period. In addition to ensure that any inaccuracy in definition of pernicious anaemia did not cause bias we carried out an analysis restricting the exposed group to patients with both a specific pernicious anaemia diagnosis code (i.e., excluding patients with vitamin B12 deficiency anaemia due to other causes)and vitamin B12 therapy. Additionally, regarding the community-acquired pneumonia outcome we looked specifically at more severe pneumonia by limiting outcomes to those coded within hospital data only.

5.3.7. Sample size calculation

A feasibility count in CPRD showed there were 38,842 cases (patients with pernicious anaemia), and that of these 312 had a record of C. difficile infection subsequent to pernicious anaemia diagnosis. Previous studies estimate that the odds ratio for C. difficile infection is above 2(119), in patients taking PPIs. Using ten controls per case, we expected to achieve 99% power to detect an effect of this size or larger in those with pernicious anaemia and to achieve >90% power using HES-linked cases alone. Similarly, using the same cases (patients with pernicious anaemia), there were 2,303 patients who had at least one diagnosis of pneumonia recorded following pernicious anaemia. Therefore, we expected to achieve 99% power to detect a hazard ratio of 1.6(108) in those with pernicious anaemia using 10 controls per case and still have similar power using only HES linked practices.

5.4. Results

5.4.1. Study population

We identified 6.6 million patients enrolled in CPRD who had at least one year of active registration from 1990 to 2013. Of this group, 66,575 patients had a diagnosis code for vitamin B12 deficiency anaemia or pernicious anaemia. Of these, 20,025

patients were excluded because they were below the age of 18 years at the start of follow-up, had less than 1 year of vitamin B12 therapy during CPRD follow-up, or had an alternative indication for use of vitamin B12 (Figure 5-1). Therefore, 45,467 patients were included in our exposed cohort. We successfully matched a total of 449,635 unexposed patients to these cases in terms of age, gender, and general practice (Table 5-1). The CPRD-HES linked information was available for 24,869 exposed patients and their 246,593 controls. A comparison of the baseline characteristics of the study population at the start of follow-up is shown in (Table 5-1) for all CPRD patients and in (Table 5-2) for the CPRD-HES linked patients. The exposed patients were more likely to have a higher burden of comorbidity and had used more medication compared to the control group.

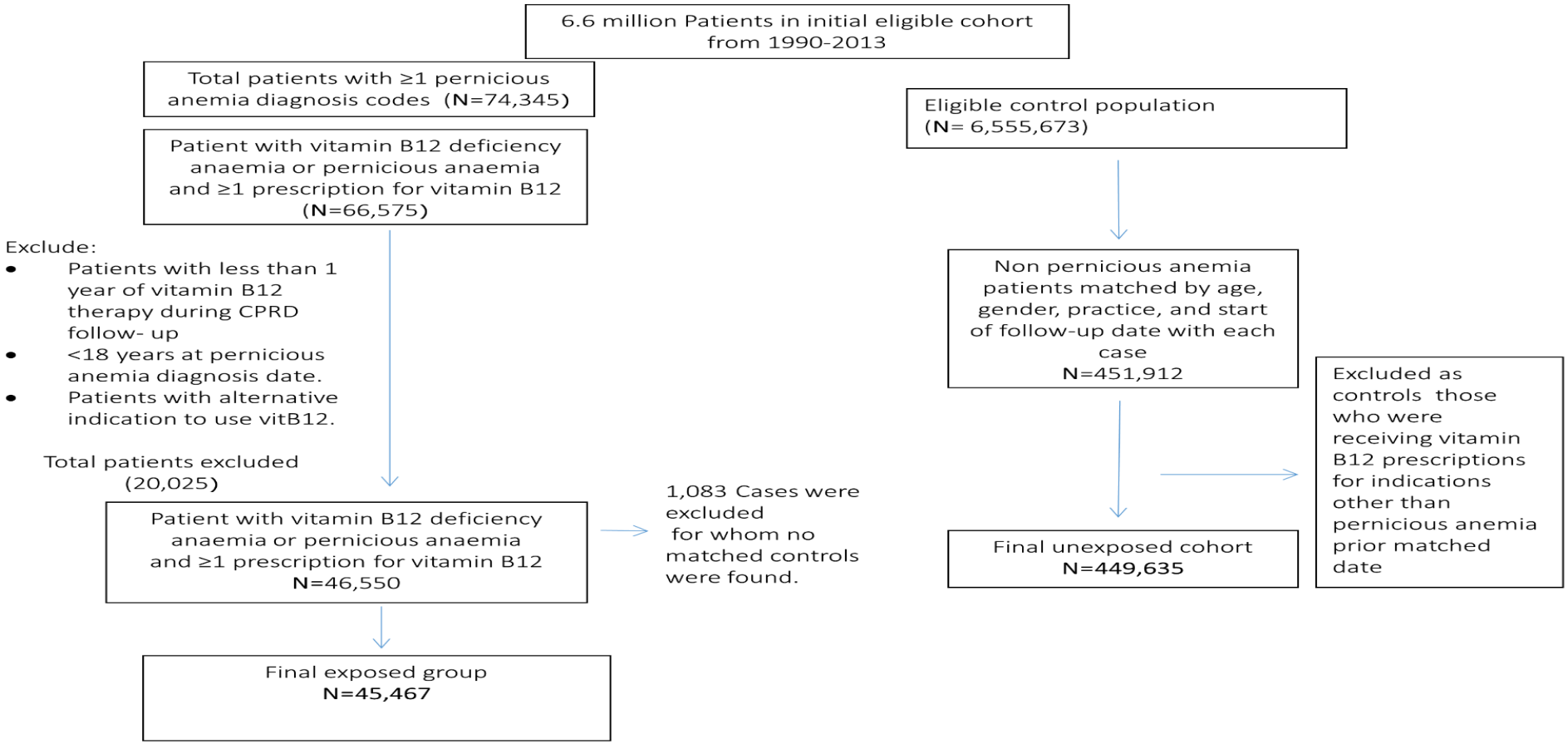

Figure 5-1 Flow diagram of patient selection from the Clinical Practice Research Datalink (CPRD) population.

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Table 5-1 Demographic and clinical characteristics of the study population included in the cohort study by exposure status at cohort entry into the study period for all CPRD patients

	Complete cohort				
	Total number of patients 495,102				
characteristic	**Unexposed 449,635**	**%**	**Exposed 45,467**	**%**	**P-value**
Age (mean SD)	64(17)		65(17)		<0.001
Smoking					<0.001
Never smoked	155,877	34	14,152	31	
smoker	122,311	27	12,810	28	
missing	171,447	38	18,505	41	
Index of Multiple Deprivation (IMD) Quintiles*					<0.001
1(least deprived)	50,695	20	4,581	18	
2	60,257	23	5,775	22	
3	53,159	21	5,277	20	
4	51,201	20	5,503	21	
5(most deprived)	42,149	16	4,848	19	
Charlson comorbidity index score					<0.001
0	200,730	45	17,029	37	
1-2	122,141	27	12,507	28	
3-4	92,608	21	10,349	23	
>5	34,156	7	5,582	12	
Medications					
Acid suppressing	70,500	16	8,993	20	<0.001
Immunosuppressant	18,641	4	2,886	6	<0.001
Corticosteroids	42,257	9	5,617	12	<0.001
Antibiotics	133,547	30	15,156	33	<0.001

* Socioeconomic status is based on Index of multiple deprivation (IMD) and figures are the percentage of the patients eligible for inclusion in the linkage to patient level deprivation data

Table 5-2 Demographic and clinical characteristics of the study population included in the cohort study by exposure status at cohort entry into the study period, for the subset of patients with CPRD-HES linked data.

	HES linked cohort				
	Total number of patients 271,462				
	Unexposed	%	Exposed	%	P-value
characteristic	246,593		24,869		
Age (mean SD)	64(17)		65(17)		<0.001
Smoking					<0.001
Never smoked	75,439	31	7,035	28	
smoker	63,914	26	6,905	27	
missing	107,240	43	10,929	44	
Index of Multiple Deprivation (IMD) Quintiles*					<0.001
1(least deprived)	38,801	20	3,505	17	
2	45,872	23	4,403	22	
3	40,284	20	4,038	20	
4	39,168	20	4,226	21	
5(most deprived)	31,840	16	3,737	19	
Charlson comorbidity index score					<0.001
0	105,860	43	8,619	35	
1-2	67,419	27	6,892	28	
3-4	53,337	22	5,973	24	
>5	19,977	8	3,385	13	
Medications					
Acid suppressing	36,531	15	4,982	20	<0.001
Immunosuppressant	6,141	2	971	4	<0.001
Corticosteroids	24,013	10	3,206	13	<0.001
Antibiotics	70,461	28	8,131	33	<0.001

HES Hospital Episode Statistics* Socioeconomic status is based on Index of multiple deprivation (IMD) and figures are the percentage of the patients eligible for inclusion in the linkage to patient level deprivation data

5.4.2. Community-acquired pneumonia results:

5.4.2.1. Primary analysis

The mean follow-up time for the unexposed cohort was slightly longer than that for the exposed patients (4.4 vs. 4.2 years). The crude incidence rate of first community-acquired pneumonia was higher among exposed patients (67.4 cases /1000 person-years of follow-up), compared to the controls (48.7/1000 person-years of follow-up). According to an unadjusted Cox regression analysis, the exposed group had a higher risk of community-acquired pneumonia than the controls with an HR of 1.38 (95%CI 1.35 to 1.40)(Table 5-3). This attenuated to 1.24 (95%CI 1.21 to 1.26) after adjusting for the confounders that altered the unadjusted model by >10% which include comorbidity index, use of acid suppression therapy, corticosteroid and immunosuppressant drugs.

For the HES subset the adjusted HR for community-acquired pneumonia was higher (HR 1.39,% CI 1.44- 1.94)(Table 5-4).

5.4.2.2. Sensitivity analyses:

An analysis restricting the exposed cohort to those patients who were diagnosed with vitamin B12 deficiency anaemia or pernicious anaemia at least 1 year after CPRD enrolment showed lower HR compared to the primary analysis (HR

1.17,95%CI 1.14 to 1.20)(Table 5-3). The results of the analysis limited to exposed group with a more specific diagnosis code of pernicious anaemia and who were on vitamin B12 therapy yielded an adjusted HR of 1.21 (95%CI 1.18 to 1.25). However, restricting the analysis to the definition of severe community-acquired pneumonia using only codes from HES data showed an increase in the adjusted HR (Table 5-5).

Table 5-3 Adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with pernicious anaemia among CPRD patients.

	The main analysis		Sensitivity analysis			
			Newly diagnosed cases with at least 1 year of follow-up in CPRD		Only cases with pernicious anaemia diagnosis code	
	Unexposed	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
Parameter	449,635	45,467	282,830	28,590	165,987	16,735
Community-acquired pneumonia event (%)	96,482 (21.4)	12,997 (28.5)	56,351 (19.92)	7,574 (26.49)	40,335 (24.30)	5,202 (31.08)
Rate of pneumonia per 1,000 person years (95%CI)	48.70 (48.39 to 49.01)	67.46 (66.31 to 68.63)	51.33 (50.91 to 51.76)	71.23 (69.65 to 72.86)	48.86 (48.39 to 49.34)	64.44 (62.71 to 66.21)
Unadjusted Hazard ratio (95%CI)	1.38 (1.35 to 1.40)		1.37 (1.34 to 1.41)		1.30 (1.26 to 1.34)	
Adjusted hazard ratio [a] (95%CI)	1.24 (1.21 to 1.26)		1.17 (1.14 to 1.20)		1.21 (1.17 to 2.25)	

CPRD, Clinical Practice Research Datalink, CI, confidence interval

* Model adjusted for comorbidity index, use of acid suppression therapy, corticosteroid and immunosuppressant drugs.

Table 5-4 Adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with pernicious anaemia among CPRD_HES linked patients

	The main analysis		Sensitivity analysis			
			Newly diagnosed cases with at least 1 year of follow-up in CPRD		Only cases with pernicious anaemia diagnosis code	
Parameter	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
	246,593	24,869	154,678	15,611	80,324	8,069
Community-acquired pneumonia event (%)	51,459 (20.87)	6,896 (27.73)	28,272 (18.28)	3,867 (24.7)	19,513 (24.2)	2,500 (30.9)
Rate of pneumonia per 1,000 person years (95%CI)	48.85 (48.43 to 49.28)	72.24 (70.55 to 73.96)	51.41 (50.81 to 52.01)	77.42 (75.01 to 79.90)	48.79 (48.11 to 49.48)	68 82 (66.17 to 71.57)
Unadjusted Hazard ratio (95%CI)	1.48 (1.44 to 1.52)		1.50 (1.45 to 1.55)		1.42 (1.35 to 1.48)	
Adjusted hazard ratio [a] (95%CI)	1.39 (1.35 to 1.43)		1.34 (1.29 to 1.39)		1.36 (1.30 to 1.42)	

CPRD, Clinical Practice Research Datalink, HES, Hospital Episode Statistics data, CI, confidence interval * Model adjusted for comorbidity index, use of acid suppression therapy, corticosteroid and immunosuppressant drugs

***Table 5-5*Adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with pernicious anaemia using only outcomes from HES data.**

	The main analysis		Sensitivity analysis			
			Newly diagnosed cases with at least 1 year of follow-up in CPRD		Only cases with pernicious anaemia diagnosis code	
Parameter	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
	246,593	24,869	154,678	15,611	80,324	8,069
Community-acquired pneumonia event (%)	8,803 (3.57)	1,262 (5.07)	4,900 (3.17)	692 (4.43)	3,399 (4.23)	463 (5.74)
Rate of pneumonia per 1,000 person years (95%CI)	8.35 (8.18 to 8.53)	13.22 (12.51 to 13.97)	8.91 (8.66 to 9.16)	13.85 (12.85 to 14.92)	8.50 (8.21 to 8.79)	12.74 (11.63 to 13.96)
Unadjusted Hazard ratio (95%CI)	1.60 (1.50 to 1.70)		1.56 (1.43 to 1.69)		1.51 (1.36 to 1.67)	
Adjusted hazard ratio [a] (95%CI)	1.53 (1.43 to 1.63)		1.43 (1.31 to 1.56)		1.48 (1.33 to 1.65)	

HES, Hospital Episode Statistics data, CI, confidence interval * Model adjusted for comorbidity index, use of acid suppression therapy, corticosteroid and immunosuppressant drug

5.4.3. C. difficile infection results:

5.4.3.1. Primary analysis

The mean follow-up time was similar in the exposed cohort and in the unexposed group (5 years in both). Overall, the crude incidence rate of C. difficile was higher among patients with a diagnosis of pernicious anaemia, 1.85 cases per 1000 persons years of follow-up, compared with matched controls, 1.09 cases per 1000 persons years of follow-up. The unadjusted Cox regression analysis revealed that the exposed group had an increased risk of C. difficile infection compared to the controls with a HR of 1.76 (95% CI 1.58 to 1.97). In the adjusted analyses of the potential confounders, the following variables altered the overall hazard ratio: comorbidity index, hospitalisation, and use of antibiotics, acid suppression therapy, and immunosuppressant drugs. Thus, after adjusting for those confounders, the HR for the association between pernicious anaemia and C. difficile infection decreased to 1.57 (95% CI 1.40 to 1.76) (Table 5-6). The adjusted HR for C. difficile infection in the HES subset was similar at 1.67 (95% CI 1.44- 1.94)(Table 5-7).

5.4.3.2. Sensitivity analyses:

The analysis of pernicious anaemia patients who had an incident diagnosis of pernicious anaemia and who were on vitamin B12 therapy yielded similar results to our primary analysis (Table 5-6). The analysis of those patients who had been diagnosed with pernicious anaemia based only on pernicious anaemia diagnosis codes and B12 injections showed a slightly higher adjusted HR(1.73 95%CI 1.41 to 2.13)

Table 5-6Adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of Clostridium Difficile infection with pernicious anaemia among CPRD patients.

	The main analysis		Sensitivity analysis			
			Newly diagnosed cases with at least 1 year of follow-up in CPRD		Only cases with pernicious anaemia diagnosis code	
	Unexposed	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
Parameter	449,635	45,467	282,830	28,590	165,987	16,735
Clostridium Difficile infection event (%)	2,492 (0.5)	429 (0.9)	1685 (0.5)	278 (0.9)	855 (0.5)	141 (0.8)
Rate of Clostridium Difficile infection per 1,000 person years (95%CI)	1.09 (1.05 to 1.13)	1.85 (1.69 to 2.04)	1.34 (1.28 to 1.49)	2.21 (1.96 to 2.49)	0.88 (0.83 to 0.94)	1.44 (1.22 to 1.70)
Unadjusted Hazard ratio (95%CI)	1.76 (1.58 to 1.96)		1.68 (1.47 to 1.92)		1.80 (1.48 to 2.18)	
Adjusted hazard ratio [a] (95%CI)	1.57 (1.40 to 1.76)		1.43 (1.24 to 1.64)		1.73 (1.41 to 2.13)	

CPRD, Clinical Practice Research Data , CI, confidence interval* Model adjusted for comorbidity index, hospitalization, and use of antibiotics, acid suppression therapy, and immunosuppressant drugs

Table 5-7 Adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of Clostridium Difficile infection with pernicious anaemia among CPRD-HES patients.

	The main analysis		Sensitivity analysis			
			Newly diagnosed cases with at least 1 year of follow-up in CPRD		Only cases with pernicious anaemia diagnosis code	
	Unexposed	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
Parameter	246,593	24,869	154,678	15,611	80,324	8,069
Clostridium Difficile infection event (%)	1,453 (0.5)	257 (1.2)	899 (0.5)	175 (1.1)	496 (0.6)	85 (1.1)
Rate of Clostridium Difficile infection per 1,000 person years (95%CI)	1.30 (1.24 to 1.37)	2.44 (2.16 to 2.74)	1.58 (1.48 to 1.68)	3.08 (2.65 to 3.57)	1.16 (1.06 to 1.27)	1.98 (1.60 to 2.44)
Unadjusted Hazard ratio (95%CI)	1.97 (1.72 to 2.26)		2.03 (1.71 to 2.40)		1.80 (1.40 to 2.30)	
Adjusted hazard ratio [a] (95%CI)	1.67 (1.44 to 1.94)		1.64 (1.36 to 1.98)		1.59 (1.21 to 2.09)	

CPRD, Clinical Practice Research Datalink, HES, Hospital Episode Statistics data, CI, confidence interval* Model adjusted for comorbidity index, hospitalization, and use of antibiotics, acid suppression therapy, and immunosuppressant drugs

5.5. Discussion

5.5.1. Summary of main findings

In this cohort study, patients with a pernicious anaemia diagnosis had an increased risk for community-acquired pneumonia compared to the control group and this risk decreased with a stricter definition of pernicious anaemia and restriction to incident diagnosis. Also, our findings suggest that pernicious anaemia patients have an increased risk of C. difficile infection of 57% and this association persisted when we limited the analysis to a subgroup with a more restrictive definition of pernicious anaemia diagnosis, or to incident cases.

5.5.2. Limitations and strengths of the study

As our study was conducted using anonymised electronic patient records, we were not able to confirm the diagnoses of both the exposure and outcomes. However, the validity of recorded diagnosis in CPRD is high (129,135,193) and a previous study has examined the diagnosis of community-acquired pneumonia in the CPRD with additional information from the linked HES data(194). This suggested that errors in the assigned diagnoses are not likely to be common. In addition, since it is unlikely any such error would be more or

less common in either group, any bias resulting is likely to merely reduce the apparent association observed. Furthermore, we have attempted to further reassure ourselves in this regard, by insisting on a record of vitamin B12 therapy to define our exposure which should have minimised the risk of misclassification. I also did our sensitivity analysis which restricted to patients with pernicious anaemia specific diagnosis codes, where this definition had been previously used in a study that utilized a similar database(75,195), and this further supports our belief that misclassification of exposure status did not have a major impact on our results. In addition, we attempted to control for a variety of confounders by employing both matching and adjustment techniques within the analysis. Although adjusting for acid suppression medication use altered the effect of estimates of community-acquired pneumonia and C. difficile infection respectively, these medications would be on the casual pathway as it have been suggested that acid suppressive medication shares the same mechanism whereby pernicious anaemia causes the outcome of this study(93,94). However, adjusting for the use of acid suppressive medication will not bias the total effect, as these medications would not alter the effect of pernicious anaemia on the outcomes through intermediate effect(196). We also considered drug exposure

variables as time-varying to maximize the ability to capture any confounding effect by these variables. Nevertheless, this study was limited to the data recorded in our dataset and it is highly unlikely that we eliminated all confounding and, as such, residual confounding may have impacted our results.

Adding to the possibility of the effect of uncorrected residual confounding, there is potential for bias with respect to missing data such as smoking status. In our analysis strategy, we included a category for missing data rather than ignoring patients with missing data. Adopting an alternative approach to handling missing data in our analysis, such as multiple imputation, would be very advantageous; however, it could also lead to misleading results because of the limited information that is available on the extent of the missing data and the mechanisms that give rise to this missing data. Thus, the underlying assumption of multiple imputation assumes that the data are missing at random; however, at any time point in a dynamic clinical database, such as CPRD, this assumption may not be correct. Although there are improvements in the data quality, the information that is available for the many variables collected in CPRD is not determined by the purpose of the research but based on each GP's assessment of what was important and relevant to the

ongoing health care of the patient. Therefore, it is possible that there are biases in terms of the areas of missing data and these may limit the extent to which the results from the application of multiple imputation to such complex data can be regarded as more reliable than any other approach (197).

However, the data employed in this study had a number of significant advantages. Firstly, the large number of records within the CPRD gave us adequate power to minimise random error. Since the data was collected independently of the research, this should greatly reduce the risk of information bias(131). Similarly, the selection of all available cases and a random subset of appropriate controls should mean that our study is free from selection bias. To further assure ourselves of this with regard to survivorship, we conducted a sensitivity analysis of incident cases. The results of this analysis were unchanged substantiality from those of the overall analysis. Finally, since the CPRD population is representative of the general UK population(131),our results are likely to be generalizable to the UK population or similar populations.

5.5.3. The inappropriateness of using the self-controlled case series analysis or the PERR adjustment method to assess the potential effect of pernicious anaemia on infections:

We used a Cox proportional hazards model to examine the association between pernicious anaemia and infections in this study. As indicated in Chapter 4, this form of analysis is not sufficient if we are concerned about the role of unmeasured confounding in explaining the observed association. We could not apply the self-controlled case series analysis or the PERR adjustment method to further examine the robustness of the observed association in this study because of the risk that some of the assumptions that need to be met for the self-controlled case series and PERR analysis methods to be considered reliable would be violated. For the self-controlled case series, the assumption that the occurrence of an event must not alter the probability of subsequent exposure would be violated in this situation. It is likely that patients who have been diagnosed with C. difficile or pneumonia would be more likely to have blood tests than those who have not; therefore, the likelihood that abnormality in haemoglobin levels would be detected and diagnosed with pernicious anaemia is higher in this population. In the case of PERR adjustment method, although it would be very useful to apply this method to

reduce the bias that results from residual confounding in the assessment of the relationship between pernicious anaemia and C. difficile infection, the validity of assumptions of PERR in this situation would limit its applicability. As is the case in the assumption for self-controlled case series I mentioned above, when a patient first develops a C. difficile infection, he or she may have more blood tests and, consequently, this will influence the likelihood that any abnormalities in haemoglobin level will be diagnosed. Hence, the probability of the exposure (diagnosis of pernicious anaemia) is definitely influenced by the previous C. difficile event. It is also possible that cases with pernicious anaemia had concomitant immunodeficiency disorders(198,199), leading to an increased risk for subsequent C. difficile infection that was independent of achlorhydria state(200). Thus, the health characteristics of the patients and consequently the unmeasured confounder effects would vary temporally between pre- and post-period; therefore, in this setting, the PERR adjustment method may generate biased results.

5.5.4. Comparison with previous literature:

Our finding suggests that pernicious anaemia is an independent risk factor for the increased risk of community-acquired pneumonia and C. difficile infection. This increased

risk is likely due, in part, to the achlorhydria and loss of the gastric acid barrier that acts against ingested pathogens that are not resistant to low pH(93,94). Lab studies have reported that gastric acid has a potent bactericidal effect at pH<4 that is capable of killing ingested bacterial pathogen(93). Researchers theorise that removing this barrier will facilitate bacterial colonisation, thereby leading to the translocation of bacteria to the upper respiratory system and the subsequent increased risk of pneumonia(96). Alternatively, in the case of C. difficile infection, a risk of the colonisation of bacteria further along the gastrointestinal tract, which will influence the gut microbiota, has also been suggested(99,201).

The chronic and persistent achlorhydria seen in pernicious anaemia is at least as marked as that generally associated with long-term PPI use. Several observational studies have reported an increased risk of community-acquired pneumonia(96,113) and C. difficile infection(120,124,125) in patients on PPI and indicated that it was the loss of the gastric acid barrier that acted as the mechanism of the observed increased risk of these infections. For C. difficile infection, two meta-analyses have shown a significant increase in the incidence of C. difficile infection among patients on PPI therapy with an overall risk estimate between 1.65 (95% CI 1.41 -

1.93)(124) and 1.74 (95%CI 1.47-2.85)(125). Although the findings of those studies that support the relationship between lesser degrees of acid suppression and C. difficile infection are consistent with the findings of the current study (HR 1.57, 95% CI 1.40 to 1.76), which may support the theory that severe hypochlorhydria could be the mechanism that increases the risk of C. difficile infection in long-term PPI users, we clearly cannot entirely draw a definite conclusion as to whether the observed association between pernicious anaemia and C. difficile does, in fact, reflect a cause-and-effect relationship. Thus, it is often difficult and very challenging to ascertain whether an identifiable risk factor is actually a cause of disease. In evaluating the possible causality of exposure on an outcome, additional criteria should be met (referred to Bradford Hill criteria for causation)(202). This includes strength of the association, consistency, specificity, temporality, the presence of a biological gradient, plausibility, coherence, experimental evidence, and analogy(202). A strong association between pernicious anaemia and C. difficile infection was identified in our study, and our findings appear to be consistent with other similar studies that have examined the role of PPIs in the development of C. difficile infection that shares the same biological mechanism (consistency) (124,125). Also, in our study design, we required the presence

of pernicious anaemia diagnosis prior to the onset of C. difficile infection (temporality). In addition, experimental studies have suggested that gastric acid has a potent bactericidal effect and, at pH<4, it is capable of killing ingested bacterial pathogen(93), and both C. difficile infection and achlorhydria are being increasingly recognised (coherence). On the other hand, this association is not at all specific in a significant number of cases of C. difficile infection in individuals who have not been diagnosed with pernicious anaemia, and not all patients who have been diagnosed with pernicious anaemia develop C. difficile infection; i.e., the specificity of the effects argues against the causal interpretation of the association. Moreover, even though the association appears biologically plausible in terms of hypochlorhydria as a mechanism; there is very limited data on the association between PPI and C. difficile infection risk that demonstrates a dose–response relationship; i.e., biological gradient.

Our finding for pneumonia is in line with a recent observational study that examined the association between pernicious anaemia and pneumonia using data from another UK computerised medical record database: The Health Improvement Network (THIN) (195). Almario et al. observed an 18% (95%CI 1.08-1.29) increase in the risk of community-acquired pneumonia in patients with pernicious anaemia

compared to those patients without a diagnosis of pernicious anaemia(195). Our results in the analysis of the subgroup of patients with our more restrictive definition of pernicious anaemia diagnosis revealed a 21% increase in community-acquired pneumonia risk, which is within the 95%CI of the finding of the previous study. This could be explained by the similarity between their definition of pernicious anaemia and our restrictive definition.

Nevertheless, for community-acquired pneumonia, many of the previous studies reported larger increases in risk after relatively short periods of exposure(96), which cannot support the biological rationale; i.e., hypochlorhydria, as the underlying mechanism for PPI to increase the risk of pneumonia. Adding to this, the association between pernicious anaemia and community-acquired pneumonia in this study is of smaller magnitude than that for C. difficile infection, it is plausible that unmeasured confounders might account for the observed association.

5.6. Conclusion

To summarise, the results of this population-based cohort study suggested that patients with pernicious anaemia should recognise that this is a risk factor for community-acquired

pneumonia and C. difficile infection. This suggests the possibility of achlorhydria as the underlying mechanism in patients with pernicious anaemia, therefore indicating that sever hypochlorhydria in chronic PPI therapy could play a role in the underlying mechanism for the increases in infection risk if C. difficile infection is causally associated. For pneumonia, we found a much smaller association. This supports my findings in the previous chapter, and further supports the conclusion that the association of pneumonia and low pH states is likely to be explained by unmeasured confounding.

Chapter Six

Overall Discussion and Conclusion

This PhD was concerned with examining the epidemiology of PPI therapy use and safety in a general population through the utilisation of a large UK-based electronic database of primary care records, the CPRD. To reiterate, the thesis had three main objectives in terms of the use of PPIs in the general population: (i) to examine the patterns of PPI use and the practices employed to reduce PPI use in the general UK population, (ii) to investigate the effect of the confounders on one of the suspected health concerns associated with PPI, community-acquired pneumonia, by using a new analytic technique known as the PERR adjustment method, and (iii) to bridge the gap in understanding of the possible mechanism by which PPI patients exhibit an increased susceptibility to infection by examining the risk of infection (community-acquired pneumonia and Clostridium difficile infection) in patients with pernicious anaemia who have a similar low stomach acidity to patients prescribed PPIs.

The key findings in response to the thesis aims are summarised in Section 6.1. Section 6.2 outlines the interpretation and clinical consequences of these findings and Section 6.3 presents a set of recommendations for further studies that are based on the findings of this research.

6.1. Summary of thesis main findings:

The three studies covered in this thesis add important knowledge to the epidemiology of PPI therapy use and different safety aspects of PPI use in the general population.

PPI prevalence in UK general practices (Chapter 3): There was a considerable increase in the administration of PPI prescriptions in UK general practice such that the prevalence of PPI use increased from 0.2% in 1990 and reached 14.8% in 2012. Of those who used PPI therapy on a long-term basis (≥1 year continuously), 41% did attempt to step down the medication; while this figure was 48% in patients whose initial indication did not mandate long-term use. There were, therefore, an appreciable proportion of long-term PPI users for who attempts to reduce or cease use might be appropriate.

The risk of community-acquired pneumonia and PPI prescription (Chapter 4): To add to the mounting body of data on the association between using PPI and community-acquired pneumonia, we examined this association using a self-controlled case series method, the Cox regression adjustment method, and the PERR method. We came to the conclusion that patients who use PPIs were at higher risk of community-acquired pneumonia prior to being exposed to them and that therefore the presence of confounders

explained the association which was observed in the previous studies.

The risk of infection (community-acquired pneumonia and C. difficile infection) in patients with pernicious anaemia (Chapter 5): The extent to which the relationship between PPI use and infection observed in previous studies is, in fact, due to hypochlorhydria was indirectly assessed in this study. I showed that pernicious anaemia increases the risk of the infections studied, the strongest association being with C. difficile infection. Hypochlorhydria, therefore, could play a role in the underlying mechanism for the increases in infection risk if C. difficile infection is causally associated. However, the association with pneumonia was much smaller and likely due to unmeasured confounding as in chapter 4.

6.2. Clinical consequences and implications

The work in this thesis provides evidence that there is a high prevalence of PPI prescribing in the primary care setting and that there has been an increase in the percentage of patients who use PPI continually for more than one year. As such, any risks that are identifiable to be associated with PPI use will have considerable impact. This reinforces current guidelines related to the use of PPI to manage dyspepsia in primary care and the need to adhere to the NICE guidelines to reduce

inappropriate instances of PPI prescription administration and the overuse of PPIs, especially in patients whose initial indication did not mandate long-term use. Adequate health care reviews have to be promoted to PPI users to optimise patient care delivery and reassess their needs for the continuation of long-term PPI therapy.

With regards to the potential risk of infections associated with PPI therapy through the suggested mechanism of the reduction of gastric acidity, the results of the cohort study described in Chapter 4 indicate that treatment with PPI does not seem to increase the risk of community-acquired pneumonia. This is reassuring for the number of patients using PPI therapy for valid reasons and is contrary to the increased risk observed in the previous observational studies. To further emphasise this point, the modest association between pernicious anaemia and community-acquired pneumonia cannot support the biological rationale, i.e hypochlorhydria, behind the large increase in risk after relatively short periods of exposure to PPI. Since PPIs cannot achieve the same level of gastric acid suppression in a short time period as that observed with pernicious anaemia it is unlikely that they would produce a greater effect via that mechanism.

A further issue for consideration is the potential consequence of the chronic hypochlorhydria associated with long-term PPI use, which is capable of altering the risk of enteric infection. The study reported in chapter 5 clearly demonstrates that there is potential for this to lead to significant enteric infections. The potential consequences of these changes should therefore be motivation for practitioners to exercise caution when administering PPIs over a long-term basis particularly to patients who have other risk factors for developing enteric infection.

6.3. Suggestions for further research

This PhD thesis employed general practice data to explore the potential adverse effects of medication without the expense of a clinical trial. It has revealed the potential and practicality of large routinely collected primary care data for future pharmacoepidemiology studies. In addition, given the continuing improvements to data quality and quantity, and the on-going efforts to link CPRD and other data sets to provide greater depth of information on patients and their medical diagnosis, there is scope for further studies in this area. There is on-going accumulation of data obtained from many studies that have assessed other acute potential adverse effects of using PPI, such as cardiovascular events(55–57), and it might

be that applying the PERR adjustment method to test these associations would be a basis for further research be worth pursuing in more depth in the future.

Despite the great benefits of using general practice data, there are a number of issues that CPRD cannot address and where the use of other methods would be needed in future studies. For example, further scientific research describing the effect of PPIs on C. difficile spore germination, effect on growth, and effects on toxin production is likely to provide additional insight into the association between prolonged PPI usage and C. difficile infection risk. In addition, this will solidify our understanding of changes caused by PPIs within the gut not only to C. difficile infection but also for other enteric infection risk.

In addition to the proposed infective complications of PPI use on which we have focussed, there are a group of effects upon electrolyte homeostasis which could also be further elucidated via CPRD. The evidence for the association between PPI use and electrolytes abnormalities(hypomagnesemia, hyponatremia, hypokalaemia, and hypocalcaemia) is based on case reports or studies involved inpatients and critically ill patients(83,84,89,203–205). Therefore, it is difficult to draw

any conclusions from these studies as they were either small in size or were hospital-based. As such, utilising the CPRD to assemble a large population-based cohort of patients who have recently been treated with long-term PPIs to examine this would provide a further step in understanding of whether PPIs are a risk factor for these outcomes in routine clinical practice. I have obtained the ISAC approval for this study (protocol number 16_165R2).

6.4. Conclusion

This thesis used primary care data that consisted of complete longitudinal records of patients' information, diagnosis and prescription within the general population. The studies in this thesis have described the utilisation of PPI therapy in the general population and clearly demonstrated that the safety concerns of community-acquired pneumonia being associated with PPI use was unfounded. However, other potential adverse effects will still be a concern, not only for PPI therapy, but also for any drugs; and with improving health care databases and enhanced pharmacoepidemiological methodologies such as the PERR, the future of this field is promising in assessing these risks using routine data.

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Appendices

Appendix 1 : Codes for potential indication for PPI use

Medcode	Readcode	Medical description within the CPRD database
134	1954	Indigestion
846	1955	Heartburn
6041	1955.11	Heartburn symptom
4643	1956	Peptic ulcer symptoms
7577	1957	Gastric reflux
43233	1958	Undiagnosed dyspepsia
5928	7627	Operations on duodenal ulcer
2812	14C1.00	H/O: peptic ulcer
6321	14C1.11	H/O: duodenal ulcer
7108	14C1.12	H/O: gastric ulcer
5862	195..00	Indigestion symptoms
37118	195Z.00	Indigestion symptom NOS
17819	4JM0.00	Helicobacter breath test positive
37913	4JN0.00	Helicobacter blood test positive
11317	760..00	Oesophagus (including hiatus hernia) operations
17263	760L.11	Oesophageal reflux operations
38633	760y.00	Oesophagus (including hiatus hernia) operations OS
41666	760z.00	Oesophagus (including hiatus hernia) operations NOS
20677	761J000	Closure of perforated gastric ulcer
5759	8BAC.00	Helicobacter eradication therapy
14928	A074313	Helicobacter gastritis
8937	A074500	Helicobacter pylori gastrointestinal tract infection
33275	A3BXJ00	Helicobacter pylori cause diseases classified other chapters
23355	C115.11	Zollinger - Ellison syndrome
45503	J1...00	Oesophageal, stomach and duodenal diseases
592	J101.00	Oesophagitis

2535	J101100	Reflux oesophagitis
15054	J101111	Acid reflux
7104	J101112	Gastro-oesophageal reflux with oesophagitis
16605	J101113	Oesophageal reflux with oesophagitis
15579	J101114	Peptic oesophagitis
4614	J101611	Barrett's oesophagus
14760	J101z00	Oesophagitis NOS
2489	J102.00	Ulcer of oesophagus
24021	J102000	Peptic ulcer of oesophagus
51013	J102200	Oesophageal ulcer due to aspirin
94752	J102300	Oesophageal ulcer due to chemicals
58603	J102400	Oesophageal ulcer due to medicines
5596	J102500	Barrett's ulcer of oesophagus
16713	J103.00	Oesophageal stricture and stenosis
41141	J103z00	Oesophageal stricture and stenosis NOS
10060	J10y300	Oesophageal erosions
25610	J10y400	Oesopheal reflux without mention of oesophagitis
1327	J10y411	Oesophageal reflux
984	J10y412	Gastro-oesophageal reflux
2281	J10y413	Acid reflux
1262	J11..00	Gastric ulcer - (GU)
3101	J11..12	Pyloric ulcer
14671	J110200	Acute gastric ulcer with perforation
71403	J110300	Acute gastric ulcer with haemorrhage and perforation
44324	J110z00	Acute gastric ulcer NOS
63582	J111100	Chronic gastric ulcer with haemorrhage
11104	J111211	Perforated chronic gastric ulcer
44309	J111z00	Chronic gastric ulcer NOS
63001	J112.00	Anti-platelet induced gastric ulcer
89227	J112z00	Anti-platelet induced gastric ulcer NOS
89023	J113.00	Non steroidal anti inflammatory drug induced gastric ulcer
53081	J11y.00	Unspecified gastric ulcer

73338	J11y000	Unspecified gastric ulcer without mention of complication
57958	J11y100	Unspecified gastric ulcer with haemorrhage
44284	J11yz00	Unspecified gastric ulcer NOS
29771	J11z.00	Gastric ulcer NOS
2877	J11z.11	Gastric erosions
352	J12..00	Duodenal ulcer - (DU)
18001	J120100	Acute duodenal ulcer with haemorrhage
18324	J120200	Acute duodenal ulcer with perforation
53822	J120y00	Acute duodenal ulcer unspecified
9853	J121.00	Chronic duodenal ulcer
33438	J121000	Chronic duodenal ulcer without mention of complication
37643	J121200	Chronic duodenal ulcer with perforation
23087	J121211	Perforated chronic duodenal ulcer
52138	J121y00	Chronic duodenal ulcer unspecified
22918	J122.00	Duodenal ulcer disease
3462	J123.00	Duodenal erosion
53669	J12y.00	Unspecified duodenal ulcer
71150	J12y000	Unspecified duodenal ulcer without mention of complication
657	J12y200	Unspecified duodenal ulcer with perforation
15175	J12z.00	Duodenal ulcer NOS
670	J13..00	Peptic ulcer - (PU) site unspecified
32856	J130.00	Acute peptic ulcer
68661	J130000	Acute peptic ulcer without mention of complication
44637	J130100	Acute peptic ulcer with haemorrhage
5521	J130200	Acute peptic ulcer with perforation
40997	J131.00	Chronic peptic ulcer
99430	J131000	Chronic peptic ulcer without mention of complication

53126	J131100	Chronic peptic ulcer with haemorrhage
37620	J131200	Chronic peptic ulcer with perforation
52313	J131400	Chronic peptic ulcer with obstruction
70390	J131y00	Chronic peptic ulcer unspecified
69663	J131z00	Chronic peptic ulcer NOS
50497	J13y.00	Unspecified peptic ulcer
70456	J13y100	Unspecified peptic ulcer with haemorrhage
64111	J13y200	Unspecified peptic ulcer with perforation
99670	J13y400	Unspecified peptic ulcer with obstruction
19928	J13z.00	Peptic ulcer NOS
23082	J14..00	Gastrojejunal ulcer (GJU)
15403	J14z.00	Gastrojejunal ulcer NOS
10906	J154400	Helicobacter gastritis
25544	J156.00	Gastroduodenitis unspecified
376	J157.00	Duodenitis
257	J16y400	Dyspepsia
7623	J16y412	Indigestion NOS
4448	R071.00	[D]Heartburn
25805	R071z00	[D]Heartburn NOS

Appendix 2 : Codes for community-acquired pneumonia

Medcode	Readcode	Medical description within the CPRD database
58896	A022200	Salmonella pneumonia
9953	A116.00	Tuberculous pneumonia
22009	A3BX400	Streptococ pneumon/cause/disease classified/oth chapters*
31024	A3BXA00	Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr*
26287	A3BXB00	Klebsiella pneumoniae/cause/disease classifd/oth chapters
51398	A3By400	Pleuropneumonia-like organism (PPLO) infection
25462	A521.00	Varicella pneumonitis
47973	A54x400	Herpes simplex pneumonia
32172	A551.00	Postmeasles pneumonia
50408	A730.00	Ornithosis with pneumonia
45072	A785000	Cytomegaloviral pneumonitis
27641	A789300	HIV disease resulting in Pneumocystis carinii pneumonia
104717	A789311	HIV disease resulting in Pneumocystis jirovecii pneumonia
40299	AB24.11	Pneumonia - candidal
101507	AB40500	Histoplasma capsulatum with pneumonia
101292	AB41500	Histoplasma duboisii with pneumonia
106031	AyuK900	[X]Mycoplasma pneumoniae [PPLO]cause/dis classifd/oth chaptr*
14308	43n1.00	Mycoplasma pneumoniae antibody level
96583	AyuKA00	[X]Klebsiella pneumoniae/cause/disease classifd/oth chapters*
6124	H062.00	Acute lower respiratory tract infection*
2581	H06z000	Chest infection NOS*
68	H06z011	Chest infection*
37447	H06z112	Acute lower respiratory tract infection*
4899	H06z200	Recurrent chest infection*
10086	H2...00	Pneumonia and influenza
5202	H20..00	Viral pneumonia
9389	H20..11	Chest infection - viral pneumonia
67836	H200.00	Pneumonia due to adenovirus
31269	H201.00	Pneumonia due to respiratory syncytial virus
36675	H202.00	Pneumonia due to parainfluenza virus
106300	H203.00	Pneumonia due to human metapneumovirus
33478	H20y.00	Viral pneumonia NEC
14976	H20z.00	Viral pneumonia NOS

1849	H21..00	Lobar (pneumococcal) pneumonia
29166	H21..11	Chest infection - pneumococcal pneumonia
28634	H22..00	Other bacterial pneumonia
22795	H22..11	Chest infection - other bacterial pneumonia
23546	H220.00	Pneumonia due to klebsiella pneumoniae
30591	H221.00	Pneumonia due to pseudomonas
37881	H222.00	Pneumonia due to haemophilus influenzae
48804	H222.11	Pneumonia due to haemophilus influenzae
12423	H223.00	Pneumonia due to streptococcus
63858	H223000	Pneumonia due to streptococcus, group B
5612	H224.00	Pneumonia due to staphylococcus
50867	H22y.00	Pneumonia due to other specified bacteria
65419	H22y000	Pneumonia due to escherichia coli
60299	H22y011	E.coli pneumonia
45425	H22y100	Pneumonia due to proteus
12061	H22y200	Pneumonia - Legionella
52384	H22yX00	Pneumonia due to other aerobic gram-negative bacteria
43884	H22yz00	Pneumonia due to bacteria NOS
23095	H22z.00	Bacterial pneumonia NOS
25694	H23..00	Pneumonia due to other specified organisms
30653	H23..11	Chest infection - pneumonia organism OS
1576	H231.00	Pneumonia due to mycoplasma pneumoniae
73735	H232.00	Pneumonia due to pleuropneumonia like organisms
17025	H233.00	Chlamydial pneumonia
34251	H23z.00	Pneumonia due to specified organism NOS
40498	H24..00	Pneumonia with infectious diseases EC
24316	H24..11	Chest infection with infectious disease EC
41034	H240.00	Pneumonia with measles
43286	H241.00	Pneumonia with cytomegalic inclusion disease
62623	H242.00	Pneumonia with ornithosis
30437	H243.00	Pneumonia with whooping cough
106908	H244.00	Pneumonia with tularaemia
34274	H246.00	Pneumonia with aspergillosis
52071	H247000	Pneumonia with candidiasis
103404	H247100	Pneumonia with coccidioidomycosis
53969	H247z00	Pneumonia with systemic mycosis NOS
69782	H24y.00	Pneumonia with other infectious diseases EC

61623	H24y000	Pneumonia with actinomycosis
67901	H24y100	Pneumonia with nocardiasis
27519	H24y200	Pneumonia with pneumocystis carinii
60482	H24y300	Pneumonia with Q-fever
72182	H24y400	Pneumonia with salmonellosis
98782	H24y500	Pneumonia with toxoplasmosis
49398	H24y600	Pneumonia with typhoid fever
23726	H24y700	Pneumonia with varicella
70559	H24yz00	Pneumonia with other infectious diseases EC NOS
66362	H24z.00	Pneumonia with infectious diseases EC NOS
886	H25..00	Bronchopneumonia due to unspecified organism
16287	H25..11	Chest infection - unspecified bronchopneumonia*
572	H26..00	Pneumonia due to unspecified organism
19400	H26..11	Chest infection - pnemonia due to unspecified organism
9639	H260.00	Lobar pneumonia due to unspecified organism
8318	H260000	Lung consolidation
3683	H261.00	Basal pneumonia due to unspecified organism
15912	H270.00	Influenza with pneumonia
29457	H270.11	Chest infection - influenza with pneumonia
13573	H270000	Influenza with bronchopneumonia
62632	H270100	Influenza with pneumonia, influenza virus identified
35745	H270z00	Influenza with pneumonia NOS
5324	H28..00	Atypical pneumonia
104121	H2B..00	Community acquired pneumonia
11849	H2y..00	Other specified pneumonia or influenza
6094	H2z..00	Pneumonia or influenza NOS
35189	H530300	Abscess of lung with pneumonia
52520	Hyu0800	[X]Other viral pneumonia
63763	Hyu0A00	[X]Other bacterial pneumonia
98381	Hyu0B00	[X]Pneumonia due to other specified infectious organisms
53947	Hyu0D00	[X]Pneumonia in viral diseases classified elsewhere
53753	Hyu0H00	[X]Other pneumonia, organism unspecified
66397	Hyu1.00	[X]Other acute lower respiratory infections*

* These codes were included in the broad primary care definition of community-acquired pneumonia

Appendix 3: Codes for Pernicious anaemia and vitamin B12 deficiency

Medcode	readcode	Medical description within the CPRD database
54738	1452	H/O: Anaemia vit.B12 deficient
2515	C262100	Vitamin B12 deficiency
2464	D010.00	Pernicious anaemia
2813	D010.11	Addison's anaemia
55370	D010.12	Biermer's congenital pernicious anaemia
29486	D011.00	Other vitamin B12 deficiency anaemias
5271	D011.11	Vitamin B12 deficiency anaemia
32953	D011000	Vitamin B12 deficiency anaemia due to dietary causes
6028	D011X00	Vitamin B12 deficiency anaemia, unspecified
31270	D011z00	Other vitamin B12 deficiency anaemia NOS
47952	Dyu0100	[X]Other dietary vitamin B12 deficiency anaemia
35092	Dyu0200	[X]Other vitamin B12 deficiency anaemias
53846	Dyu0600	[X]Vitamin B12 deficiency anaemia, unspecified
24581	F11x600	Cerebral degeneration due to vitamin B12 deficiency
56973	F381500	Myasthenic syndrome due to pernicious anaemia

Appendix 4: Codes for Clostridium difficile infection

medcode	readcode	Medical description within the CPRD database
10716	4JD2000	Clostridium difficile toxin A detected
38115	683B.00	Clostridium difficile toxin detection
6700	A3Ay200	Clostridium difficile infection
37022	J431311	Pseudomembranous colitis
8645	J434.00	Pseudomembranous colitis
70718	J521.12	Pseudomembranous colitis

Appendix 5: ICD 10 codes in Hospital Episodes Statistics for pneumonia outcome

description	ICD-10
Varicella pneumonia	B012
Measles complicated by pneumonia	B052
HIV disease resulting in Pneumocystis carinii pneumonia	B206
Influenza with pneumonia, influenza virus identified	J100
Influenza with pneumonia, virus not identified	J110
Adenoviral pneumonia	J120
Respiratory syncytial virus pneumonia	J121
Parainfluenza virus pneumonia	J122
Other viral pneumonia	J128
Viral pneumonia, unspecified	J129
Pneumonia due to Streptococcus pneumoniae	J13
Pneumonia due to Haemophilus influenzae	J14
Pneumonia due to Klebsiella pneumoniae	J150
Pneumonia due to Pseudomonas	J151
Pneumonia due to staphylococcus	J152
Pneumonia due to streptococcus, group B	J153
Pneumonia due to other streptococci	J154
Pneumonia due to Escherichia coli	J155
Pneumonia due to other aerobic Gram-negative bacteria	J156
Pneumonia due to Mycoplasma pneumoniae	J157
Other bacterial pneumonia	J158
Bacterial pneumonia, unspecified	J159
Chlamydial pneumonia	J160
Pneumonia due to other specified infectious organisms	J168
Pneumonia in bacterial diseases classified elsewhere	J170
Pneumonia in viral diseases classified elsewhere	J171
Pneumonia in mycoses	J172
Pneumonia in parasitic diseases	J173

Pneumonia in other diseases classified elsewhere	J178
Bronchopneumonia, unspecified	J180
Lobar pneumonia, unspecified	J181
Hypostatic pneumonia, unspecified	J182
Other pneumonia, organism unspecified	J188
Pneumonia, unspecified	J189
Abscess of lung with pneumonia	J851
Viral pneumonia, not elsewhere classified	J12
Human metapneumovirus pneumonia	J123
Bacterial pneumonia, not elsewhere classified	J15
Pneumonia due to other infectious organisms, not elsewhere classified	J16
Pneumonia in diseases classified elsewhere	J17
Pneumonia, organism unspecified	J18

List of publication from the work in this thesis

Peer Reviewed Journal Publications

Othman F, Card TR, Crooks CJ. Proton pump inhibitor prescribing patterns in the UK: A primary care database study. Pharmacoepidemiol Drug Saf. 2016 Sep;25(9):1079–87.

Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. BMJ. 2016;355:i5813.

Othman F, Crooks CJ, Card TR. The risk of Clostridium difficile infection in patients with pernicious anaemia: a retrospective cohort study using primary care database. United Eur Gastroenterol J. SAGE PublicationsSage UK: London, England; 2017 Jan;205064061769569.

Conference Presentations

Othman F, Crooks CJ, Card TR .2015. Proton pump inhibitors and the risk of pneumonia using a new analytical technique: results from a retrospective cohort study using primary care database. Abstract presented at 23rd United European Gastroenterology Week; 2015 Oct 26-28; Barcelona, Spain (Vol 3, Issue 5_suppl, pp. A 90).

Othman F, Card TR, Crooks CJ. 2016.Proton pump inhibitor prescribing patterns in the UK: A primary care database study. Poster presented at: Saudi Student Conference; 2016 Feb 13-14; Birmingham, UK.

Othman F, Crooks CJ, Card TR. 2016. The risk of Clostridium Difficile infection in patients with pernicious anaemia: a retrospective cohort study using primary care database. Abstract presented at: 24th United European Gastroenterology Week; 2016 Oct 17-19; Vienna, Austria (Vol 4, Issue 5_suppl, pp. A 73)