JIM Original Article

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doi: 10.1111/joim.12826

Use of proton pump inhibitors and risk of iron deficiency: a population-based case–control study

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Abstract. Tran-Duy A, Connell NJ, Vanmolkot FH, Souverein PC, de Wit NJ, Stehouwer CDA, Hoes AW, de Vries F, de Boer A (Maastricht University Medical Center, Maastricht, the Netherlands; University of Melbourne, Melbourne, Australia; Maastricht University, Maastricht; Utrecht University; University Medical Center Utrecht, Utrecht, the Netherlands). Use of proton pump inhibitors and risk of iron deficiency: a population-based case–control study. *J Intern Med* 2019; **285**: 205–214.

Background. Hypochlorhydric states are an important cause of iron deficiency (ID). Nevertheless, the association between therapy with proton pump inhibitors (PPIs) and ID has long been a subject of debate. This case–control study aimed to investigate the risk of ID associated with the use of PPIs using the UK Clinical Practice Research Datalink (CPRD) database.

Methods. Cases were patients aged 19 years or older with first-time diagnosis of ID between 2005 and 2016 (n = 26 806). The dates of first diagnosis of ID in cases defined the index dates. For each case, one control was matched by age, gender and general practice. A PPI "full" user (PFU) was defined as a subject who had received PPIs for a continuous duration of at least 1 year prior to the index date. A PPI "limited" users (PLU) was a subject who intermittently received PPI therapy. A PPI non-user (PNU) was a subject who received no PPI prescriptions prior to the index date. The odds ratio of ID in PFU and PLU compared to PNU was estimated using conditional logistic regression.

Results. Among cases, 2960 were PFU, 6607 PLU and 17 239 PNU. Among controls, 1091 were PFU, 5058 PLU and 20 657 PNU. Adjusted odds ratio of ID in PFU and PLU compared to PNU was 3.60 (95%CI, [3.32–3.91]) and 1.51 (95% CI, [1.44–1.58]). Positive dose–response and time–response relationships were observed.

Conclusions. Chronic PPI use increases the risk of ID. Physicians should consider this when balancing the risks and benefits of chronic PPI prescription.

Keywords: acid suppressant, drug safety, iron deficiency, pharmacovigilance, proton pump inhibitor.

Introduction

Iron deficiency is frequently diagnosed in primary health care. Since iron is essential for haemoglobin synthesis, iron deficiency is the most common cause of microcytic anaemia, which is associated with clinical symptoms such as pallor of the skin, fatigue, headache, and exertional dyspnoea [1, 2]. Globally, anaemia affected more than 2.2 billion people in 2010, of which roughly 50% was attributable to iron deficiency. Iron deficiency may lead to decreased work productivity and, in exceptional cases, pose serious health risks such as cognitive impairment, decreased work productivity and mortality due to severe anaemia [1–3].

Hypochlorhydric states have long been known as an important cause of iron deficiency. While the association between iron deficiency and hypochlorhydria induced by atrophic gastritis and partial gastrectomy has been well-established [2, 4], it is less clear whether the achlorhydria induced

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by proton pump inhibitors (PPIs) causes iron deficiency [5, 6]. So far, no large population-based studies have been conducted to assess the association between PPI use and the risk of iron deficiency. PPIs are widely prescribed in clinical practice for the treatment of dyspepsia, gastro-oesophageal reflux disease and peptic ulcer disease, and often co-prescribed in patients using nonsteroidal anti-inflammatory drugs (NSAIDs), low dose aspirin or other drugs that are associated with an increased risk for upper gastro-intestinal bleeding (UGIB) [7]. There is increasing evidence showing that PPIs are overprescribed in both primary and secondary care. It is estimated that between 25% and 70% of PPI users do not have an evidence-based indication [8–10]. Given the widespread use of PPIs, the benefits of PPI use should be weighed against the harms. Recently, concern has been expressed about the increasing number of potential adverse effects of long-term PPI use, one of which is the risk of iron deficiency [11, 12].

So far, there has been little evidence supporting the recommendations for systematic monitoring of body iron stores in patients receiving PPI therapy [11, 13]. In the present study, we aimed to assess the association between therapy with PPIs and iron deficiency using a large sample size from the UK Clinical Practice Research Datalink (CPRD) Gold.

Methods

Study design and setting

We conducted a case–control study using the CPRD Gold, one of the largest primary care databases in the world. Up to 2015, the CPRD database contains over 11 million patients, who are representative of the UK population in terms of age, gender and ethnicity [14]. Data recorded in this database include demographic information, prescriptions, clinical diagnoses, specialty consultation notes, and hospital discharge diagnoses. The diagnoses and drug prescriptions are coded using the Read codes and the Product codes, respectively [14–16]. Patients included in the CPRD database from 1998 to the latest data collection (June 2016) were used as the source population for our study.

In the present study, we hypothesized that the hypchlorhydria induced by PPIs impairs adequate absorption of iron and consequently increases the risk of iron deficiency. Because histamine type 2 receptor antagonists (H2RA) also suppress gastric acid secretion, subjects receiving one or more prescriptions of these drugs (see Product codes in Table S1 in the Supplement) before the index date were excluded from source population. Among antacids, sodium bicarbonate- and calcium carbonate-based substances may interfere with iron absorption after long-term use [17]; therefore, subjects receiving these antacids (see Product codes in Table S2) for a continuous period longer than 90 days before the index date were also excluded from the source population.

Sample size

The sample size was calculated using the software tool Power and Sample Size Calculation (version 3.1.2, 2014) based on the methods of Dupont [18, 19]. In anticipation that a large number of cases would be identified from the source population, we decided to select one control for each case. The Type I error (α) was set at 0.05 and a power of 0.8 was assumed. The probability of exposure to PPIs in controls (p_0) was estimated to be 0.025 based on the prescription rate of PPIs in the CPRD Gold database. Based on limited data from the literature, the odds ratio of exposure in cases relative to controls (ψ) was estimated to be 2.5 [5, 6]. We found no information in the literature about the correlation coefficient for exposure between matched cases and controls (Φ). In an extreme scenario, i.e. the scenario that requires a very large sample size to detect the effect of PPI use, we set ψ at 1.5 and Φ at 0.7 (against the suggested value of 0.2 when Φ is unknown) [18]. With these parameter estimates, a sample size of 6980 cases or larger, and the same number of controls are sufficient.

Case ascertainment

In 2004, the national Quality and Outcomes Framework (QoF) became effective in the UK, which aimed to improve the quality of care by rewarding practices for the quality of care they provide to their patients. One of the main components of the QoF is Clinical Domain, which consists of indicators that require records of risk factors of a wide range of diseases. To obtain high-quality data and minimize the chance of having missing risk factors, we set the time window of analysis between 2005 and the latest data collection year (2016) [20]. From the source population, cases were identified as patients aged 19 years or older with a first time diagnosis of iron deficiency (see Read codes in Table S3) after 31th of December, 2004 and who

had received at least one prescription of iron supplement (see Product codes in Table S4) within 30 days after the first diagnosis of iron deficiency. The date of the first diagnosis of iron deficiency defined the index date.

Selection of controls

For each case, one control was randomly selected from the source population using incidence density sampling and matched to the corresponding case by year of birth, sex and general practice. Controls were defined as individuals who had no iron deficiency on and no history of iron deficiency before the index date of the matched case. The matched controls were assigned the same index date as the case.

Exposures

Exposures to PPIs were identified using Product codes (see Table S5). Based on literature [21] and opinion of experts in pharmacology, we assumed that a continuous duration of PPI use of 1 year or more is necessary to deplete the body iron store, and that a period of 3 months or longer is sufficient for the replenishment of depleted iron stores in an individual with a normal gastric pH level. Therefore, a patient fully exposed to PPIs (PPI full user, PFU) was defined as an individual who received PPIs for a continuous duration of at least 1 year prior to the index date, with the time gap (if any) between the index date and the last date of this continuous duration shorter than 90 days. A continuous duration of PPI use was defined as a period within which the time gap (if any) between the last date of PPI use in a prescription and the starting date of the next prescription was shorter than 30 days. This 30-day time gap was based on patient behaviour of taking the drugs and estimated time needed to replenish the body's iron stores. In reality, patients do not always adhere to their prescriptions; instead, they can stop and restart their medication as they feel necessary. In the case of PPIs, the period of drug use can be extended up to 30 days after the last date of PPI use in the prescription. Also, the 30-day period is deemed insufficient to replenish the body's iron stores through normal dietary intake. Figure 1 depicts the definitions of a PPI full user.

Individuals who received at least one prescription of PPI prior to the index date, but did not meet the criteria for PFU were defined as PPI limited users (PLU). Individuals who received no prescription of PPIs prior to the index date were defined as PPI nonusers (PNU).

Theoretically, only the last period of continuous PPI use with the time gap between the last date of this period and the index date shorter than 90 days could contribute to the risk of iron deficiency. To analyse the effect of dosage of PPI use on the risk of iron deficiency, the cumulative dosage of PPIs of this last period (in PFUs or PLUs) was calculated based on the number of prescriptions, the prescribed doses, and the time window of each prescription. We standardized PPI dosage using the definition by the World Health Organization [22], where one defined daily dose (DDD) is equivalent to 20 mg omeprazole, 40 mg pantoprazole, 30 mg lansoprazole, 20 mg rabeprazole, 30 mg esomeprazole or 30 mg dexlansoprazole. Patients were classified into groups with 0.10–0.99, 1.00–1.99, 2.00–2.99, and ≥3.00 DDDs based on the average DDD over the last period of continuous PPI use. Similarly, the effect of the duration of PPI use on iron deficiency was analysed by classifying

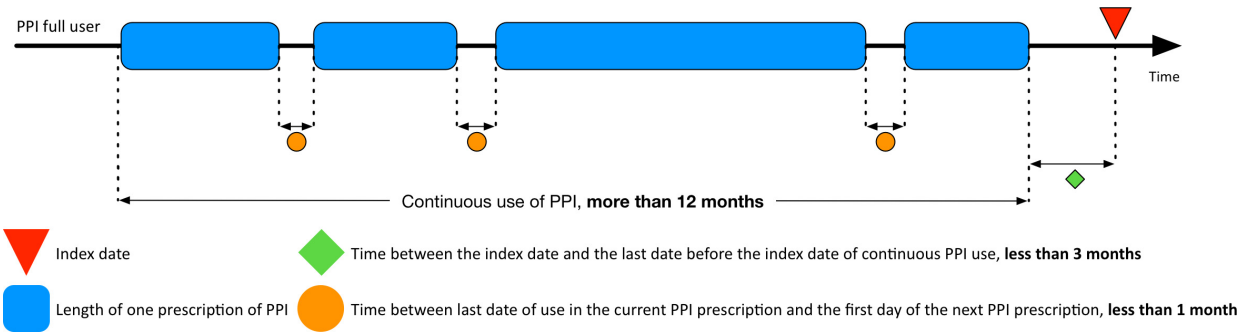

Fig. 1 *Definition of a full user of proton pump inhibitors.*

patients into groups with the above-mentioned period of 0.10–0.99, 1.00–1.99, 2.00–2.99, and ≥3.00 years. PLUs with the time gap between the index date and the last date of last period of PPI use longer than 90 days, and PNUs were considered as non-exposed subjects and assigned to the group with average DDDs of 0 and to the group with a duration of PPI use of 0 years.

Outcome

The outcome of the present study was the first occurrence of iron deficiency in PFUs and PLUs compared to PPI nonusers.

Covariates

The risk factors for the development of iron deficiency that could confound the relationship between PPI use and iron deficiency were determined based on literature [1, 2, 23, 24] and opinion of experts in internal medicine and pharmacology, and identified for each case or control based on the Read codes. These factors were grouped into six categories (Table 1); each group represents a single mechanism that may cause iron deficiency. Therefore, models were adjusted for the following covariates (see Read codes in Tables S6–S11): (i) chronic disease (occurring at any time before the index date); (ii) definite blood loss (occurring within 3 months before the index date); (iii) inflammatory bowel disease (occurring at any time before the index date); (iv) malabsorption, including also vegetarian or vegan diet (occurring at any time before the index date); (v) possible lower gastro-intestinal blood loss (occurring within 3 months before the index date); and (vi) possible upper gastro-intestinal blood loss (occurring within 6 months before the index date).

Statistical analysis

Characteristics of the cases and controls were analysed using descriptive statistics. Conditional logistic regression was used to estimate the odds ratios (ORs) of iron deficiency associated with different levels of PPI exposure. The model was adjusted for the covariates described previously. If a covariate independently changed the beta-coefficient for PPI use by at least 5%, it was included in the multivariable model. To determine the dose–response and time–response relationships, the model was also adjusted for dummy variables representing different levels of average DDD and cumulative duration of PPI use, respectively. The data compilation and statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, USA).

Table 1 *Covariates grouped by mechanism of action*

Chronic disease [2, 4, 23, 24] (CD)	Chronic kidney disease stages 4 and 5, malignant neoplasm of any origin, rheumatoid arthritis, ankylosing spondylitis, heart failure
Definite blood loss [2, 4] (DBL)	Menorrhagia, blood donation, rectal blood loss, melena
Inflammatory bowel disease [2, 4] (IBD)	Ulcerative colitis, Crohn's disease
Malabsorption [2, 4] (MAL)	Blind loop syndrome, small bowel bacterial overgrowth syndrome, vegetarian or vegan diet, gastrectomy, pernicious anaemia, gastric bypass, short bowel syndrome, Helicobacter gastritis, coeliac disease
Possible lower gastro-intestinal blood loss [2, 4] (PLGIBL)	Meckel's diverticulum, diverticulosis, diverticulitis, colorectal polyp, haemorrhoids, Trichuriasis, Hookworm, malignant neoplasm of caecum, sigmoid colon, anal canal or small intestine
Possible upper gastro-intestinal blood loss [2, 4] (PUGIBL)	Gastric or duodenal polyp or angiodysplasia, duodenal or gastric ulcer, Barrett's oesophagus, oesophagitis, upper gastrointestinal malignant neoplasm, gastro-oesophageal reflux, gastritis, hematemesis

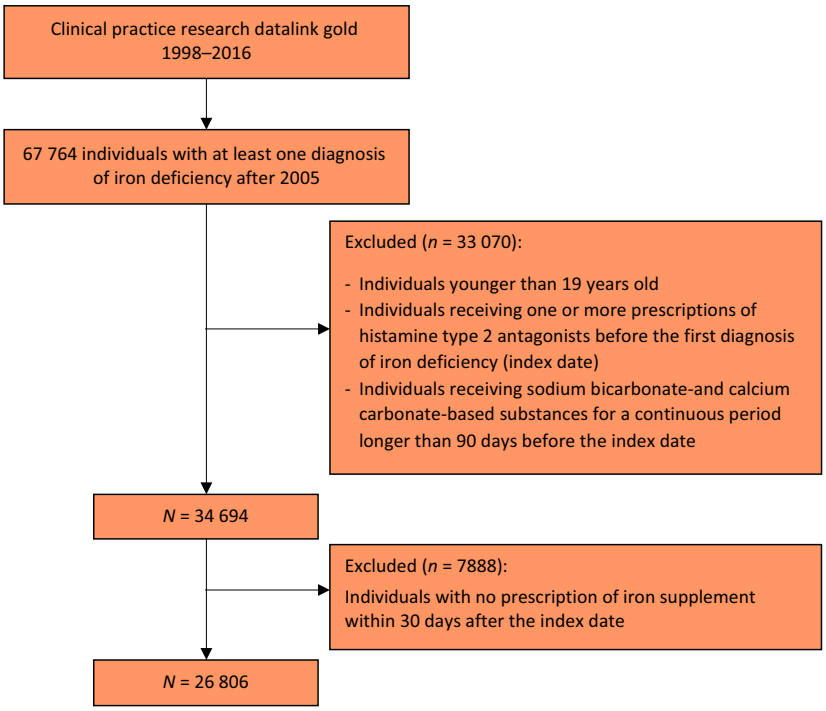

Fig. 2 *Flowchart of case selection.*

Results

Figure 2 shows the flowchart of case selection in the present study. The source population consisted of 67 764 individuals with at least one diagnosis of iron deficiency after 31th of December, 2004. After applying the inclusion and exclusion criteria, we found 26 806 cases, who were adequately matched to 26 806 controls. No patients contained missing data for any of the variables of interest.

Table 2 provides a summary of the characteristics of the study population. The majority of the study population was female (75.3%, n = 40 344). At baseline, the mean age of cases or controls was 58 (range: 19–108) years. Notably, patients aged 80 years or above accounted for nearly a quarter (n = 6546 in cases or controls) of the study population.

The proportions of PFUs, PLUs or PNUs in cases and controls are significantly different (P-value < 0.001). Similarly, the proportions of patients with any of the conditions represented by the covariate groups in cases and controls differed (P-value < 0.001).

Table 3 provides an overview of the DDDs and durations of exposure to PPIs. Within PFUs, mean DDDs [95% CI] in cases and controls were 1.57 [1.55–1.59]) and 1.49 [1.46–1.53], respectively, and mean duration of exposure [95% CI] in cases and controls were 3.10 [3.07–3.13] years and 3.10 [3.04–3.15] years, respectively. Within PLUs, mean DDDs [95% CI] in cases and controls were 0.97 [0.94–1.00] and 0.45 [0.43–0.48], respectively, and mean duration of exposure [95% CI] in cases and controls were 0.50 [0.49–0.51] years and 0.27 [0.25–0.28] years, respectively.

The crude ORs [95% CI] of iron deficiency in PFUs and PLUs compared to PNUs were 3.88 [3.58–4.20] and 1.73 [1.65–1.81], respectively. Compared to PLUs, the crude OR [95% CI] of iron deficiency in PFUs was 2.24 [2.07–2.43]. These values show that increasing levels of exposure to PPIs were associated with increased risk of iron deficiency.

In the adjusted model, each of the covariates independently changed the beta-coefficient for PPI use by more than 5%. Therefore, all covariates were included in the final model, which resulted in highly significant beta-coefficients for any covariate (P-value < 0.0001) but the adjusted ORs were similar to the crude estimates. The adjusted ORs [95% CI] of iron deficiency in PFUs and PLUs compared to PNUs were 3.60 [3.32–3.91] and 1.51

Table 2 *Patient characteristics*

	Case (n = 26 806)	Control (n = 26 806)
Gender, n (%)		
Male	6634 (24.7)	6634 (24.7)
Female	20 172 (75.3)	20 172 (75.3)
Age at index date, n (%)		
19–59 years	14 266 (53.2)	14 266 (53.2)
60–79 years	5994 (22.4)	5994 (22.4)
≥80 years	6546 (24.4)	6546 (24.4)
Level of PPI exposure, n (%)		
PFU[a]	2960 (11.0)	1091 (4.1)
PLU[b]	6607 (24.7)	5058 (18.9)
PNU[c]	17 239 (64.3)	20 657 (77.0)
Covariate, n (%)		
CD	3349 (12.5)	2471 (9.2)
DBL	1327 (5.0)	81 (0.3)
IBD	436 (1.6)	185 (0.7)
MAL	1080 (4.0)	501 (1.9)
PLGIBL	489 (1.8)	122 (0.5)
PUGIBL	1944 (7.3)	529 (2.0)

PPI, proton pump inhibitor; PFU, proton pump inhibitor full user; PLU, proton pump inhibitor limited user; PNU, proton pump inhibitor nonuser; CD, chronic disease; DBL, definite blood loss; IBD, inflammatory bowel disease; MAL, malabsorption; PLGIBL, possible lower gastro-intestinal blood loss; PUGIBL, possible upper gastro-intestinal blood loss.
[a]Subject receiving PPIs for a continuous duration of at least 1 year prior to the index date, with the time gap between the index date and the last date of PPI use ≤3 months. [b]Subject receiving PPI therapy prior to the index date but not fulfilling the criteria for a PFU. [c]Subject receiving no PPIs prior to the index date.

Table 3 *Exposure characteristics*

	No. of patients	
Classification	Case	Control
PPI full users[a]	2960	1091
Defined daily dose		
0.10–0.99	1406 (47.5%)	587 (53.8%)
1.00–1.99	1439 (48.6%)	464 (42.5%)
2.00–2.99	109 (3.7%)	39 (3.6%)
≥3.00	6 (0.2%)	1 (0.1%)
Duration of exposure (years)		
0.10–0.99	0 (0%)	0 (0%)
1.00–1.99	1023 (34.6%)	374 (34.3%)
2.00–2.99	613 (20.7%)	237 (21.7%)
≥3.00	1324 (44.7%)	480 (44.0%)
PPI limited users[b]	6607	5058
Defined daily dose		
0.00	3313 (50.1%)	3709 (73.3%)
0.10–0.99	1285 (19.5%)	683 (13.5%)
1.00–1.99	1315 (19.9%)	489 (9.7%)
2.00–2.99	302 (4.6%)	80 (1.6%)
≥3.00	392 (5.9%)	97 (1.9%)
Duration of exposure (years)		
0.00	3313 (50.1%)	3709 (73.3%)
0.10–0.99	3294 (49.9%)	1349 (26.7%)
1.00–1.99	0 (0%)	0 (0%)
2.00–2.99	0 (0%)	0 (0%)
≥3.00	0 (0%)	0 (0%)
PPI non-users[c]	17 239	20 657

PPI, proton pump inhibitor.
[a]Subject receiving PPIs for a continuous duration of at least 1 year prior to the index date, with the time gap between the index date and the last date of PPI use ≤3 months. [b]Subject receiving PPI therapy prior to the index date but not fulfilling the criteria for a PPI full user. [c]Subject receiving no PPIs prior to the index date.

[1.44–1.58], respectively. Compared to PLUs, the adjusted OR [95% CI] in PFUs was 2.39 [2.19–2.60].

Dose–response relationship

Table 4 shows the relationship between PPI dosage and the risk of iron deficiency. When the non-exposed individuals or patients with average DDDs between 0.10 and 0.99 were taken as a reference, ORs in patients with higher DDD levels were statistically significant, and increased with increasing contrast between the comparators. The highest OR [95% CI] was 4.09 [3.22–5.19] when patients with average DDDs ≥ 3 were compared to nonexposed subjects, and the lowest OR [95% CI] was 1.04 [0.82–1.31] when patients with average DDDs between 2.00 and 2.99 were compared to those between 1.00 and 1.99. Remarkably, patients with average DDDs between 0.10 and 0.99 had a significantly higher risk of iron deficiency compared to nonexposed subjects (OR, 2.60; 95% CI, [2.41–2.81]). Among patients with average DDDs higher than 1.00, an increase in the dosage did not further increase the risk of iron deficiency.

Table 4 *Relationship between proton pump inhibitor dosage and risk of iron deficiency*

Mean DDDs	Odds ratio	95% confidence interval
Reference: Nonexposed subjects		
0.10–0.99	2.60[a]	2.41–2.81
1.00–1.99	3.56[a]	3.27–2.88
2.00–2.99	3.70[a]	2.96–4.62
≥3.00	4.09[a]	3.22–5.19
Reference: mean DDDs between 0.10 and 0.99		
1.00–1.99	1.37[a]	1.23–1.52
2.00–2.99	1.42[a]	1.13–1.79
≥3.00	1.57[a]	1.23–2.01
Reference: mean DDDs between 1.00 and 1.99		
2.00–2.99	1.04	0.82–1.31
≥3.00	1.15	0.89–1.47
Reference: mean DDDs between 2.00 and 2.99		
≥3.00	1.10	0.80–1.52

DDD, defined daily dose with one DDD equivalent to 20 mg omeprazole, 40 mg pantoprazole, 30 mg lansoprazole, 20 mg rabeprazole, 30 mg esomeprazole or 30 mg dexlansoprazole.
[a]Statistical significance at a significance level of 0.05.

Table 5 *Relationship between the length of last period of continuous proton pump inhibitor use and risk of iron deficiency*

LPCU (years)	Odds ratio	95% Confidence interval
Reference: Nonexposed subjects		
0.10–0.99	2.69[a]	2.49–2.90
1.00–1.99	3.61[a]	3.17–4.12
2.00–2.99	3.26[a]	2.77–3.29
≥3.00	3.83[a]	3.40–4.31
Reference: LPCU between 0.10 and 0.99 years		
1.00–1.99	1.34[a]	1.16–1.55
2.00–2.99	1.21[a]	1.02–1.44
≥3.00	1.42[a]	1.25–1.62
Reference: LPCU between 1.00 and 1.99 years		
2.00–2.99	1.11	0.91–1.36
≥3.00	1.06	0.90–1.26
Reference: LPCU between 2.00 and 2.99 years		
≥3.00	1.18	0.97–1.43
Reference: LPCU < 1.00 years		
≥1.00	3.11	2.87–3.37

LPCU, last period of continuous proton pump inhibitor use with the time gap between the last date of this period and the index date shorter than 90 days.
[a]Statistical significance.

Time–response relationship

Table 5 showed the relationship between the length of the last period of continuous PPI use and the risk of iron deficiency. Patients with a period of PPI use of 3 years or longer, or with a period between 2.00 and 2.99 or between 1.00 and 1.99 years had a higher risk of iron deficiency compared to nonexposed patients or to patients with a period of PPI use shorter than 1 year. Notably, risk of iron deficiency in patients with a period of PPI use between 0.10 and 0.99 years was higher than in nonexposed individuals (OR, 2.69; 95% CI, [2.49–2.90]). Among patients with a period of PPI use longer than 1 year, an increase in the length of PPI use did not further increase the risk of iron deficiency.

Discussion

The present study showed a clear association between iron deficiency and PPI use in terms of both duration of treatment and PPI dosage. Compared to the nonexposed subjects or to patients with a period of continuous use of PPIs less than 1 year, continuous use of PPIs for 1 year or longer increased the risk of iron deficiency. Over the period of continuous use of PPIs, patients with an average dosage of PPIs of 1 DDD (equivalent to 20 mg omeprazole) or larger had a higher risk of iron deficiency compared to patients with an average dosage of less than 1 DDD. However, a dosage higher than 1 DDD did not further increase the risk.

At the time this study was designed, previous research had yielded inconclusive results about the association between PPI use and iron deficiency in the general population. Stewart *et al.* found that in a cohort of 109 patients with Zollinger-Ellison syndrome (ZES), the proportions of patients with iron deficiency did not differ between PPI users (n = 89) and PPI non-users (n = 11) [5]. However, this observation cannot be generalized for several reasons. First, no correction for potential confounders was made. Second, the sample size was too small, especially the number of PPI non-users. Finally, the study was conducted among ZES patients, whose gastric hypersecretion may attenuate the effect of PPIs on iron absorption. In a retrospective cohort study by Sarzynski *et al.*, a

decrease in haematocrit and haemoglobin was found following long-term PPI use; however, iron deficiency as the final outcome was not assessed in this study and it would be hard to conclude that PPIs causes iron deficiency based on the above-mentioned surrogate outcomes [6]. Several studies, on the other hand, supported PPI use as a cause of iron deficiency. Hutchinson *et al.* and van Aerts *et al.* observed that among patients with hereditary hemochromatosis, PPI users required fewer phlebotomies compared to PPI non-users [25, 26]. In addition, Hutchinson *et al.* conducted a postprandial iron absorption study following a case review in 15 hereditary hemochromatosis patients receiving PPIs, and concluded that PPIs prohibited the uptake of nonhaem iron from a test meal and the habitual diet [25]. Ajmera *et al.* reported the suboptimal response to ferrous sulphate supplement therapy in patients with iron deficiency who also received a PPI, which suggests an impaired uptake of nonhaem iron caused by PPI use [27]. Recently, in a large community-based case–control study by Lam *et al.*, an association between acid suppressing medication use and an increased subsequent risk of iron deficiency was observed [28]. Our results confirm the positive association between chronic PPI use and the increased risk of iron deficiency anaemia.

In recent years, it has become increasingly recognized that the majority of PPI prescriptions lack a clear indication and are often unnecessarily prolonged [29–31]. There is increasing evidence of adverse events associated with long-term PPI use, such as hypomagnesaemia [32], enteric infections [33], cobalamin deficiency [34], chronic kidney disease [35], fundic gland polyps [36] and gastric cancer [37, 38]. Therefore, it is crucial to increase vigilance when prescribing PPIs and adhere to existing guidelines.

Current clinical guidelines lack recommendation on routine monitoring of iron status in patients receiving (long-term) PPI therapy [7, 11, 13]. In the existing literature, routine monitoring of the iron status is recommended only in the frail and elderly patients [12, 27].

Our findings suggest that physicians prescribing PPIs for a duration of more than a year should be aware of the risk for developing iron deficiency and consider routine monitoring of haemoglobin levels in patients with suspected symptoms. Future research is needed to determine whether this is a cost-effective strategy. Furthermore, physicians should also check if patients with iron deficiency are receiving PPIs so that appropriate measures to minimize the consequences of iron deficiency can be determined.

Strengths and limitations of study

Strengths of this study include the use of a large population-based sample size of 53 612 patients, adequate ascertainment for cases (requiring both a diagnosis of iron deficiency and a subsequent prescription of iron supplement), a clear definition of exposure (PNU, PLU and PFU), the exclusion of patients who use other anti-secretory drugs than PPIs, and adjustment of the outcomes for important confounding factors. With these strengths, and given that the patients in the CPRD Gold are representative of the UK population, our findings would be valid at the national level and probably for the Western countries.

In observational studies, confounding by indication is often a major problem that can only be partly amended because of a lack of full information on all the prognostic factors that influence the treatment decision [39]. In our study, covariates in the "possible upper gastro-intestinal blood loss" group included conditions that might lead to blood loss and therefore be associated with iron deficiency and lead to prescriptions for PPIs. Although these conditions were identified based on an extensive review of literature and consultancy of expert opinion, it cannot be excluded that the effect of PPIs might be confounded by unknown prognostic factors [39].

In this study the occurrence of iron deficiency was identified using the date of diagnosis. However, an iron deficient status might be present long before the iron deficiency was diagnosed, as body iron store is not routinely monitored in clinical practice. As a consequence, iron deficiency may in fact have occurred prior to the use of PPIs, thus possibly introducing bias into the study results. However, given the observed positive dose- and time-responses, the influence of this possible source of bias would be small.

In the exposure definitions, we assumed that the effect of PPIs on acid production was homogenous among patients having the same dosage and period of use. In reality, the ways of PPI intake (e.g. before or after meals, or the distribution of pills over time)

may vary widely which influence the pattern of acid production and hence iron absorption. There is also pharmacological heterogeneity due to different rates of PPI metabolism in the liver by CYP enzymes [40]. Because PPIs are sensitive to the CYP enzymes, there are fast and slow PPI metabolizers with different levels of systemic drug exposure [41]. As the pharmacodynamic response to PPIs is related to their systemic exposure, the gastric pH is more elevated in the fast PPI metabolizers [41]. These factors that affect acid production were not recorded in the CPRD database, and future studies that could take these into account would be valuable in affirming the association between PPI therapy and iron deficiency.

Conclusions

Long-term PPI use is associated with iron deficiency. It is therefore recommended that physicians remain vigilant when prescribing patients with PPIs for more than a year and consider the presence of iron deficiency in PPI users with suspected symptoms.

Acknowledgements

We thank the anonymous reviewers of the Independent Scientific Advisory Committee (ISAC) of the UK Medicines & Healthcare products Regulatory Agency (MHRA) for their constructive feedback on the protocol of this study (protocol number: 16_073).

Funding sources

This study was supported by a grant from The Netherlands Organization for Health Research and Development (ZonMw; Rational Pharmacotherapy Program; Project number 836021018).

Conflict of interest statement

All authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Product codes used to identify prescriptions of histamine type 2 receptor antagonists.

Table S2. Product codes used to identify prescriptions of sodium bicarbonate- and calcium carbonate-based substances.

Table S3. Read codes used to identify patients with iron deficiency.

Table S4. Product codes used to identify prescriptions of iron supplement.

Table S5. Product codes used to identify prescriptions of proton pump inhibitors.

Table S6. Read codes used to identify patients with chronic diseases.

Table S7. Read codes used to identify patients with definite blood loss.

Table S8. Read codes used to identify patients with inflammatory bowel disease.

Table S9. Read codes used to identify patients with malabsorption.

Table S10. Read codes used to identify patients with possible lower gastro-intestinal blood loss.

Table S11. Read codes used to identify patients with possible upper gastro-intestinal blood loss■

