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Hip Fracture Risk in Patients with a Diagnosis of Pernicious Anemia

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Abstract

Background & Aims—Pernicious anemia (PA) is characterized by vitamin B12 deficiency and achlorhydria, both of which have a detrimental effect on bone strength. The principle aim of this study was to determine the risk of hip fracture in patients with PA.

Methods—This is a retrospective cohort study using the General Practice Research Database (GPRD) from the United Kingdom. GPRD data from May 1987 until April 2002 were utilized to identify patients between 40 and 90 years of age at the time of GPRD enrollment. The exposed group contained patients with a diagnosis of PA being treated with vitamin B12 therapy. We matched each patient having a diagnosis of PA with 4 randomly selected non-PA patients with respect to age (+/− 1 year) and sex. Cox regression analysis was used to determine the hazard ratio (HR) for hip fracture associated with PA.

Results—9,506 patients with a diagnosis of PA receiving vitamin B12 injection therapy were identified and compared to 38,024 controls. Patients with PA had a greater risk of hip fracture than the controls (HR 1.74, 95% CI 1.45–2.08). The increase in hip fracture risk was even more pronounced among those patients newly diagnosed with PA during GPRD follow-up (HR 2.63, 95% CI 2.03–3.41).

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Conclusions—Patients with a diagnosis of PA have an elevated risk of hip fracture. The increased hip fracture risk was persistent even years after vitamin B12 therapy. Chronic achlorhydria could be the mechanism contributing to the persistently elevated hip fracture risk.

Keywords

Pernicious anemia; vitamin b12; osteoporosis; hip fracture

Introduction

Pernicious anemia (PA) is an autoimmune disease characterized by the development of auto-antibodies to intrinsic factor and gastric parietal cells, leading to vitamin B12 deficiency and achlorhydria. Both vitamin B12 deficiency and achlorhydria have been implicated in abnormal bone formation and potentially weakened bone strength. Vitamin B12 is integral to bone development and specifically to proper osteoblast function, with *in vitro* studies demonstrating that vitamin B12 deficiency is associated with osteoblast dysfunction.^{1, 2} The clinical impact of vitamin B12 deficiency on bone health has been demonstrated in population studies showing lower bone mineral density and greater fracture risk in patients with vitamin B12 deficiency.^{3, 4} Furthermore, vitamin B12 deficiency is associated clinically with peripheral neuropathy, a potential risk factor for falling. However, in a two-year randomized controlled trial, repletion of B12 resulted in an 80% reduction in hip fracture risk among stroke patients.⁵ Importantly, this effect was independent of a change in fall risk. Therefore, induction of fall risk may explain only a portion of the increase in fracture risk due to B12 deficiency, and much of this risk increase is still likely mediated through a direct effect on bone strength.

The other significant clinical manifestation of PA is achlorhydria caused by auto-antibody destruction of gastric parietal cells. This inherent gastric acid suppression leads to three pathways that are thought to negatively impact bone health: further vitamin B12 malabsorption, hypergastrinemia, and calcium malabsorption. Hypergastrinemia has been shown to stimulate parathyroid activity in animal models and in humans resulting in hyperparathyroidism and increased bone turnover.^{6–8} Calcium malabsorption has been demonstrated in animal models with gastric acid suppression,^{9, 10} as well as in humans with achlorhydria under fasting conditions.¹¹ However, the degree of calcium malabsorption in patients with achlorhydria is somewhat controversial, since Eastell et al¹² found normal calcium absorption with meals in patients with PA and achlorhydria. These processes likely result in an overall decrease in bone strength over time in patients with achlorhydria.

An important parallel group of patients with chronic gastric acid suppression are those patients taking proton pump inhibitors (PPIs). Several studies in patients taking PPIs have demonstrated similar findings to those in patients with PA and achlorhydria, including decreased vitamin B12 absorption, hypergastrinemia, and calcium malabsorption.^{13–17} Furthermore, several,^{18–20} but not all,²¹ recent observational studies demonstrated a significantly elevated risk of hip fracture in patients on long-term PPIs. Given their shared physiologic characteristics, elucidating the association between PA and fracture risk can also advance our understanding of the potential mechanisms underlying the effect of gastric acid suppressive therapy on bone health.

In terms of the risk of fracture in patients with PA, there has been only one small observational study of 131 patients diagnosed with PA from 1950 through 1979 that suggested a possible link between PA and elevated fracture risk.²² This limited study was not able to utilize the more modern confirmatory serologic auto-antibody tests for PA and was not able to control for multiple potential confounders associated with osteoporosis and fracture risk. In particular, one of the more notable potential confounders among patients with PA is the concomitant

vitamin B12 deficiency, and this study was not able to evaluate the impact of vitamin B12 treatment over time in patients with PA. Moreover, the study utilized a comparison group composed of a historic population from the community rather than a contemporary control group.

The aim of our study is to compare hip fracture risk between a large cohort of patients with PA and a control population of patients without PA while adjusting for multiple potential confounders. Our hypothesis is that even after controlling for potential confounders, there will be an increased risk of hip fracture in patients with PA. A secondary aim of our study is to explore the impact of vitamin B12 therapy on hip fracture risk over time.

Materials and Methods

Study Design

We conducted a retrospective cohort study utilizing the General Practice Research Database (GPRD). The protocol for this study was approved by the University of Pennsylvania Institutional Review Board and the GPRD Independent Scientific Advisory Committee.

Data source

The GPRD is a computerized medical record database system for general practitioners in the United Kingdom (UK) that was first established in May 1987.²³ The database contains prospective information from more than 700 general practices in the UK, and the geographic distribution of the practices and the demographic distribution of the patients are representative of the UK population.²⁴ Universal health care in the UK enables general practitioners to provide primary health care, refer patients to specialists, admit patients for hospitalization, and prescribe medications for 98% of the population in the UK. The medical records of the general practitioners therefore allow a detailed, prospective collection of demographic information, prescription patterns, clinical diagnoses from outpatient visits, hospitalizations, and specialist consultations.²⁵ Smoking histories are available on most patients, and body mass index (BMI) calculations are available on many patients. Of note, medical diagnoses prior to GPRD enrollment are recorded in addition to original event dates. Oxford Medical Information System (OXIMS) codes and Read codes are used to store the clinical diagnoses for each patient.^{26, 27} These coding systems are organized by organ system and disease type and allow efficient storage of diagnostic codes in an easily accessible and reliable format. General practitioners in the GPRD follow predetermined protocols for the recording and transferring of clinical data into the centralized database. Data quality is monitored through routine audits of GPRD practices to ensure that at least 95% of prescribing and morbidity events are included in the database. The GPRD uses a practice-based quality marker known as “up-to-standard” to indicate when data recording by the practice complied with specific quality measures according to GPRD Recording Guidelines with respect to completeness, continuity, and plausibility of data recording. We only used data that were collected after the up-to-standard date in each practice to maximize the validity of the study. There have been numerous validation studies that have confirmed the high quality of the prescription records, medical diagnoses, and documentation in the GPRD.^{23, 28}

Selection of study cohort (Figure 1)

From the more than 9.4 million patients in the GPRD from May 1987 until April 2002, we initially identified all patients between the ages of 40 and 90 years old at the time of GPRD enrollment and at least one year of up-to-standard follow-up in GPRD. Based on diagnosis codes and dates for hip fractures, those patients with a hip fracture prior to or on the date of GPRD enrollment were excluded from the study (n=3,112). The remaining subjects (n=2,704,687) composed the eligible study cohort.

Selection of exposed group

Laboratory results pertinent to the diagnosis of PA (e.g. intrinsic factor and parietal cell antibodies, Schilling test results, and vitamin B12 levels) are not available within GPRD, so the combination of a diagnosis code of PA (OXIMS code 2810 or Read code D010.00) and vitamin B12 injection prescriptions were used as the criteria to define patients in the exposed group. All patients with a diagnosis code of PA within the eligible study cohort were identified, and the initial date of diagnosis of PA (whether it occurred prior to or during GPRD follow-up) was recorded. Those with less than 1 year of vitamin B12 therapy during GPRD follow-up were excluded in order to enhance the specificity of the PA diagnosis. Patients with PA diagnosed during GPRD follow-up who had a hip fracture prior to the initial date of PA diagnosis were excluded from the study. The final exposed group consisted of patients with a PA diagnosis code who had received at least one year of vitamin B12 injection therapy within GPRD. Subcutaneous vitamin B12 injection was the primary form of vitamin B12 repletion therapy for patients with PA in the UK prior to and during the GPRD study period. Of note, to further increase the validity of the PA diagnosis codes, a subgroup of patients newly diagnosed with PA after one year of GPRD follow-up was identified and used in a secondary analysis. Follow-up time in patients with PA began either at the time of GPRD enrollment or at the PA diagnosis date within GPRD for those who were diagnosed with PA following GPRD enrollment. The end of the follow-up period was defined by a hip fracture or by patient exit from GPRD follow-up.

Selection of unexposed group

All patients in the study cohort without a diagnosis code of PA were initially identified as potential controls (n= 2.7 million). Because there were significant age and sex disparities between the PA and non-PA patients in the study cohort, we matched each PA patient with 4 randomly selected non-PA patients with respect to age (± 1 year) and sex. Start of follow-up time in the controls started at the time of GPRD enrollment. The end of the follow-up period was defined by a hip fracture or by patient exit from GPRD follow-up.

Outcome

The primary outcome in this study was time to first hip fracture during the respective follow-up period of the comparison groups.

Statistical Analysis

The baseline characteristics at study entry were compared between the patients with and without PA. The crude incidence of hip fracture in each comparison group was estimated by dividing the number of incident hip fractures in the group by the total person-years of follow-up in the same group. The primary analysis used a Cox regression model to estimate the adjusted and unadjusted hazard ratios (HRs) and accompanying 95% confidence intervals (95% CI) for risk of hip fracture in patients with and without PA.

There are many possible confounders in this study that could affect the risk of osteoporosis or the risk of falling, both of which contribute to the risk of a traumatic hip fracture. We examined the following potential confounding patient characteristics and medical conditions: sex, age, body mass index (BMI) (ie., <20, 20–30, >30, missing), the last recorded smoking status before the end of follow-up period (i.e., current, past, never, unknown), diabetes mellitus, autoimmune thyroid disease, myocardial infarction, asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, chronic renal disease, Cushing's disease, thyroid disease, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, cirrhosis, celiac sprue, Paget's disease, osteomalacia, hyperparathyroidism, dementia, vision loss, stroke, seizures, and peripheral neuropathy. Potentially confounding medications included: vitamin B12 therapy, anxiolytics,

antidepressants, thiazide diuretics, corticosteroids, hormone replacement therapy, statins, multivitamins, opiates, proton pump inhibitors, histamine-2 receptor antagonists, bisphosphonates, calcitonin, anticonvulsants, thyroxine, and calcium and vitamin D supplements.

Potential confounders were controlled for in the Cox regression analysis if the prevalence of the confounder was greater than 0.25% in either study group at the start of follow-up and if its inclusion in the respective Cox model changed the sex- and age-adjusted HR by more than 10%. This approach has been shown by Mickey and Greenland to be superior to other methods of selecting confounders in observational studies.²⁹ We used time-varying covariates for diagnosis and drug-related covariates. Specifically, each patient's follow-up time was first converted into year-long blocks of time, and the covariate status was determined for each yearly block. Each medical diagnosis was converted to bivariate format for each year of follow-up based on if and when a diagnosis occurred for a patient. In addition, medications that require chronic exposure in order to have an effect on osteoporosis risk (e.g. thiazide diuretics, corticosteroids, or hormone replacement therapy) were considered as being actively used during a given year-long follow-up block if there were at least 6 months of prescription data for the medication in a follow-up block. Medications with a more acute effect on falling risk (e.g. anxiolytics, opiates, or antidepressants) were considered as being actively used if there was a prescription for the medication within 30 days of censor date for each block.

A subgroup analysis was performed of a specific patient subset within the exposed group with similar Cox regression models. The exposed group in this analysis included those patients newly diagnosed with PA after one year of follow-up within GPRD. The choice of a one year interval after GPRD enrollment originated from a prior study by Lewis et al.³⁰ that demonstrated greater reliability of a chronic illness diagnosis code in GPRD after 12 months of follow-up. In addition, because of the increased availability of intrinsic factor antibody testing in more recent years, and the fact that such tests are much less costly and cumbersome than the traditional Schilling test, a newly made incident PA diagnosis may be more valid than a prevalent PA diagnosis. The control group for this secondary analysis remained the same.

All statistical analyses were performed using STATA 8.0 (College Station, TX, USA). Statistical significance was defined by a *p* value of less than 0.05.

Results

We identified 9,544 patients with a diagnosis of PA who had received vitamin B12 therapy for at least one year within GPRD. All but 38 (0.4%) of the 9,544 patients with a diagnosis of PA were each matched with 4 sex- and age-comparable non-PA patients (*n*=38,024). The 38 PA patients for whom no matched controls could be found were excluded from further analysis (figure 1). The mean follow-up time was comparable among the controls compared to the patients with a diagnosis of PA (5.31 years vs. 5.17 years).

A comparison of the baseline characteristics between the patients with a diagnosis of PA and those without any diagnosis of PA is shown in Table 1. The patients with a diagnosis of PA were more likely to have potentially confounding medical diagnoses than the control group. There were a significant number of patients with and without a PA diagnosis who did not have either weight or height recorded in GPRD, and therefore BMI values were missing for these patients (46.6% vs. 57.1%). For smoking status, we had 40% missing among the controls and 27% missing among the PA patients.

Overall, the crude incidence rate of first hip fracture was higher among patients with a diagnosis of PA, 3.4 hip fractures/1000 person-years of follow-up, compared to controls, 2.0 hip fractures/1000 person-years of follow-up. In unadjusted Cox regression analysis, the exposed

group (i.e., having a diagnosis of PA and having received at least 1 year of B12 therapy) had an increased risk of hip fracture compared to the controls with a HR of 1.63 (95% CI 1.36–1.96). This HR increased slightly to 1.73 (95% CI 1.45–2.08) after adjusting for age at enrollment and sex. None of the additional potential confounders altered the sex- and age-adjusted HR by more than 10 %. Therefore, none of these covariates were included in the final Cox regression model.

An analysis restricting the exposed group to those patients who were diagnosed with PA at least one year after GPRD enrollment and then started on vitamin B12 injection therapy was also conducted. This analysis included a significantly lower but still substantial number of patients with PA (n=2,708), with a total of 68 hip fractures in the group and over 10,950 person-years of follow-up. With this more strictly defined group of patients with an incident diagnosis of PA, the unadjusted Cox regression analysis yielded an HR of 2.24 (95% CI: 1.73–2.91). Further adjustment for age and sex resulted in a higher HR of 2.63 (95% CI: 2.03–3.41). Similar to the analysis including both incident and prevalent PA patients, none of the potential confounders changed the age- and sex-adjusted HR by more than 10%, and therefore, none was included in the final model.

In order to examine the impact of initiating vitamin B12 treatment on hip fracture risk among PA patients, we then compared the risk of hip fracture within each year following the diagnosis of PA in this subgroup of patients newly diagnosed with PA to the hip fracture risk among the controls (Table 3). Except for the 2nd year, the increased risk of hip fractures appeared to persist well beyond 5 or more years after the diagnosis of PA and initiation of B12 therapy. Once again, in these Cox regression analysis confined to specific blocks of follow-up periods, few potential confounders, if any, altered the sex- and age adjusted HR by more than 10% (see footnote in Table 3). By combining the third through the tenth years of follow-up to examine the fracture risk after the risk drop in the second year, the resulting age- and sex-adjusted HR was 2.96 (95% CI: 2.19–4.00).

Discussion

Patients with a diagnosis of PA have an increased risk of hip fracture compared to a control group from the same general UK population within the GPRD even after accounting for potential confounders. This risk increase was even more pronounced when the analysis was restricted to those patients newly diagnosed with PA after one year of GPRD follow-up. In addition, the increased risk of hip fracture among patients with a diagnosis of PA persisted after B12 repletion.

There has been only one previous observational study of fracture risk in patients with PA. The study observed that patients newly diagnosed with PA demonstrated an increased risk of hip fracture that was 1.9 times that of a standardized historical comparison population from the same community.²² Important limitations acknowledged by the authors of the study included the small sample of 131 patients with PA yielding only 20 total hip fractures in the study group as well as the inability of the study to control for multiple potential confounders other than age and sex. Specifically, the study was also not able to explore the yearly fracture risk after vitamin B12 therapy due to the limited power of the study. Of note, this study also included patients with prior hip fractures in their analysis, so this group included higher risk patients at baseline in terms of risk of hip fracture.

Taking advantage of an enormous population-based electronic medical record system, our study addressed the limitations of the previous study and adds a substantial amount of new information to this line of research. In our analysis of patients newly diagnosed with PA after at least one year of GPRD follow-up and started on vitamin B12 injection therapy, we noted

some very interesting results. Overall, this group of patients with PA had a greater risk of hip fracture than the controls both during the immediate period after their PA diagnosis and well beyond 5 years after initiation of B12 therapy. The reason for the transient disappearance of risk elevation during year #2 is unclear, but there is a possibility that this finding was due to chance. The potential mechanisms responsible for the persistence of elevated hip fracture risk after B12 repletion are not clear, although it is consistent with the presence of mechanisms other than vitamin B12 deficiency mediating the fracture risk.

Given that the two main clinical manifestations of PA are vitamin B12 deficiency and achlorhydria, a possible pathway for the persistently increased hip fracture risk after the correction of vitamin B12 deficiency could be the continued achlorhydria. A related group of patients with chronic gastric acid suppression are those taking long-term proton pump inhibitors (PPIs), and these patients have been found to have an increased risk of hip fracture in three prior population based observational studies.^{18–20} One of these studies was also conducted in GPRD.²⁰ While no definitive conclusions should be drawn from such comparisons, it is interesting to note that the magnitude of the hip fracture risk increase associated with long-term high daily dose PPI therapy in that GPRD study was comparable to the adjusted HR observed among the newly diagnosed PA patients in our study. However, another study, also conducted in GPRD, but only among those without major risk factors for hip fractures, failed to show an increase in the risk of hip fracture associated with PPI use, raising the question of residual confounding or effect modification in the overall association.²¹ In an attempt to exclude patients with risk factors for hip fracture, this study left out all patients with decreased bone mineral density or prior fractures.²¹ Since these risk factors are also potential mediators in the causal pathway between PPI therapy and hip fracture, excluding patients based on these factors may have contributed to the null findings. Mechanistically, gastric acid suppression has been associated with malabsorption of calcium in multiple animal and human studies,^{9–11, 17, 31} and calcium malabsorption over time can lead to a negative calcium balance and decreased bone strength. However, there have been some studies suggesting that calcium malabsorption is not significantly impaired among patients with gastric acid suppression.^{12, 32, 33} Another potential mechanism is hypergastrinemia, which has been associated with increased parathyroid activity and increased bone turnover.^{8, 34, 35} It is challenging to fully characterize the pathways leading to increased fracture risk in patients with achlorhydria due to the multiple downstream effects of chronic gastric acid suppression, but the processes underlying this association need to be better understood to help guide recommendations for prevention and treatment of osteoporosis and fractures in patients with chronic gastric acid suppression.

There are several potential limitations to our study. A definitive diagnosis of PA requires a positive Schilling test or intrinsic factor antibody result. Although we did utilize the vitamin B12 injection prescription data within GPRD to help make our exposure criteria more accurate, exposure misclassification was possible, with patients with a PA diagnosis code merely having low B12 but not actually having PA. We did not have data to assess the extent of such misclassification. If PA is truly associated with increased fracture risk, this type of misclassification would have biased the results towards the null if the factors that led to misdiagnosis of PA in our study did not by themselves impact the risk for hip fractures. However, conditions such as inflammatory bowel disease, peptic ulcer disease resulting in gastrectomy, celiac disease, alcoholism and PPI use might cause B12 deficiency, potentially resulting in misdiagnosis of PA in our cohort and at the same time increase the risk of fractures. Misdiagnosis of PA due to these conditions may bias the results towards a positive association. To assess this possibility, we repeated our primary analysis after excluding patients with these conditions that might have led to misclassification of PA status. After excluding patients with inflammatory bowel disease, peptic ulcer disease, celiac disease, alcoholism, and PPI use in our cohort, the age- and sex-adjusted HR for our primary analysis was 1.73 (95% CI: 1.43–

2.10) and the corresponding adjusted HR for the analysis restricted to newly diagnosed PA patients was 2.63 (95% CI 1.98–3.50). Except for the slightly wider CIs, these point estimates are identical to those of our original analysis. Additionally, because we excluded patients with a diagnosis of hip fracture prior to GPRD follow-up, those patients diagnosed with PA prior to GPRD enrollment who were included in our exposed group may have had an inherently lower hip fracture risk, which would further attenuate the risk associated with PA in our primary analysis. Also, exposure misclassification may be less likely to have occurred among PA diagnoses made after GPRD enrollment than those made before enrollment because of the increasing availability of intrinsic factor antibody testing during the GPRD follow-up period. Indeed, when we used a potentially more reliable definition of PA (i.e., PA diagnosed at least 1 year after GPRD enrollment), the strength of the association between PA and hip fracture increased, suggesting that we may have underestimated the true effect of PA on hip fracture risk in our primary analysis. In any case, misclassification of PA status should not diminish the clinical importance of our findings. It is possible that B12 deficiency due to causes other than PA is associated with increased fracture risk as well. Future studies are needed to examine this possibility. In the meantime, our results suggest a need for increased vigilance for the risk of osteoporotic fracture in patients requiring B12 therapy in general.

Residual confounding is an important concern in an observational study such as this. Although we matched the PA and non-PA groups with respect to age and sex, as a whole, the patients with PA still had more chronic illnesses than the control group. Adjustment for these potential confounders in the Cox regression analysis can control for confounding to some extent, and there was a sufficient amount of covariate distribution overlap between the two comparison groups (see table 1) to enable an effective adjusted analysis. We also used time-varying covariates to account for changing covariate status over the relatively long observational period in order to maximize our ability to capture any confounding effect of these variables. Furthermore, inflammatory bowel disease, peptic ulcer disease resulting in gastrectomy, celiac disease, alcoholism and PPI use may be associated with both B12 deficiency and osteoporosis, but exclusion of patients with these risk factors resulted in virtually no change in our results (see above). In addition, we noted that age and sex appeared to have accounted for nearly all the confounding effect because the comprehensive list of other potential confounders we examined changed the sex- and age-adjusted HRs minimally, either when they were included individually or simultaneously (data not shown) in the Cox regression model. This suggests negligible individual or combined confounding effect of these variables. Nevertheless, we clearly cannot entirely exclude the possibility of residual confounding. Furthermore, we were only able to adjust for variables that we could measure. Therefore, there is also the possibility of unmeasured confounding.

Another limitation is the large amount of missing BMI and smoking data. However, when a restriction analysis was performed excluding all patients with missing BMI or smoking data, there was a minimal decrease in the risk of hip fracture in patients with PA compared to the controls (HR 1.53, 95% CI 1.16–1.99). There is a risk of outcome misclassification in our study, but we deliberately selected hip fractures as the outcome since they are symptomatic, acute, and require urgent medical attention. A final limitation is that the GPRD does not have information regarding over-the-counter use of calcium or vitamin D supplements.

Our study is the largest study of the risk of osteoporotic fractures in patients with a diagnosis of PA to date, and our results suggest that PA should be considered a risk factor for osteoporotic hip fractures. We cannot determine from our data whether the increased risk was partially related to vitamin B12 deficiency, but the persistence of significantly increased risk of hip fracture years after vitamin B12 deficiency is corrected suggests another mechanism that is possibly related to the chronic achlorhydria in patients with PA. Clinically, patients with PA should continue to receive vitamin B12 supplementation and should have periodic bone density

evaluations to monitor for osteoporosis even after initiation of B12 therapy. Future prospective studies are needed to investigate the mechanistic impact of gastric acid suppression on osteoporosis and fracture risk. Potential mechanisms to be studied in such a trial include measurement of the effect of gastric acid suppression on bone metabolism, parathyroid hormone levels, calcium absorption, and vitamin B12 levels. It is important to further evaluate the mechanisms involved in the association between gastric acid suppression and fracture risk not only for patients with PA and achlorhydria but also for the increasing number of patients taking long-term PPIs that induce potent gastric acid suppression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow diagram of patient selection from GPRD

Table 1

Patient characteristics at start of GPRD follow-up*

	Non-PA patients (n=38,024)	Patients with diagnosis of PA and treated with B 12 (n=9,506)
Age at start of follow-up (yr), mean (SD)	72 (11.4)	72 (11.4)
Female, % (n)	66.43 (25,260)	66.43 (6,315)
Current Smokers, % (n)	16.39 (6,233)	21.2 (2,020)
BMI (kg/m ²)		
<20	3.06 (1,164)	6.01 (571)
20–30	33.72 (12,820)	40.50 (3,850)
>30	6.05 (2,301)	6.86 (652)
Unknown	57.17 (21,739)	46.63 (4,433)
Medical Comorbidities (#)		
Asthma	3.57 (1,358)	6.09 (579)
COPD	4.98 (1,894)	8.49 (807)
IBD	0.33 (124)	1.99 (189)
Celiac Sprue	0.07 (26)	0.82 (78)
CHF	1.17 (443)	2.60 (247)
Diabetes	1.59 (603)	3.33 (317)
Rheumatoid arthritis	0.94 (357)	2.67 (254)
Alcoholism	0.16 (60)	0.58 (55)
Myocardial infarction	2.90 (1,102)	4.73 (450)
Peptic ulcer disease	3.09 (1,175)	5.41 (514)
CVA	1.91 (728)	3.82 (363)
Vision loss	0.23 (86)	0.62 (59)
Impaired mobility	0.78 (267)	1.60 (152)
Seizure disorder	0.78 (298)	1.83 (174)
Dementia	1.23 (467)	2.27 (216)
Peripheral neuropathy	0.05 (20)	0.34 (32)
Medication Use (#)		
Acute Opiate	1.28 (487)	2.91(277)
Acute Antidepressant	4.30 (1,636)	7.74 (736)

	Non-PA patients (n=38,024)	Patients with diagnosis of PA and treated with B 12 (n=9,506)
Acute Anxiolytic	9.44 (3,590)	15.42 (1,466)
Acute Anticonvulsant	0.88 (334)	1.71 (163)
Vitamin D	0.20 (76)	0.78 (74)
Thyroxine	2.29 (870)	11.10 (1,055)
Thiazide	4.56 (1,735)	5.00 (475)
Corticosteroid	1.27 (484)	2.61 (248)
Statin	0.37 (141)	0.47 (45)
PPI	0.73 (279)	1.26 (120)
NSAID	6.41 (2,438)	9.08 (863)
HRT	0.63 (240)	0.85 (81)
Calcium	0.26 (100)	0.72 (68)
H2RA	2.96 (1,126)	3.56 (338)
Antiparkinson	1.10 (419)	1.81 (172)
Multivitamin	0.41 (154)	1.00 (95)

Abbreviations: COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; CHF, congestive heart failure; CVA, cerebrovascular accident; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; HRT, hormone replacement therapy; H2RA, histamine-2 receptor antagonist

* Values are expressed as percentages unless otherwise indicated. Dichotomous variables with a prevalence of less than 0.25% in both PA and control groups were omitted.

Table 2

Hip fracture hazard ratios according to PA status

	Non-PA	Any diagnosis of PA treated with B12	Newly diagnosed PA treated with B12
Total patients	38,024	9,506	2,708
# hip fractures	404	167	68
Total person-years	201,818	49,113	10,950
Unadjusted HR (95% CI)	Reference	1.63 (1.36–1.96)	2.24 (1.73–2.91)
Adjusted HR (95% CI, p)*	Reference	1.74 (1.45–2.08)	2.63 (2.03–3.41)

Abbreviations: CI, confidence interval; HR, hazard ratio; PA, pernicious anemia

* Adjusted for age and sex only because none of the other potential confounders examined changed the sex- and age-adjusted HR by more than 10% in analyses using either definition of PA diagnosis.

Table 3

Adjusted hazard ratios for hip fractures associated with PA newly diagnosed at least one year after GPRD enrollment in each year of follow-up after diagnosis

	Total # hip fractures/total person-years	Adjusted HR* (95% CI)
Controls: Year 1 after GPRD start	52 / 38,848	Reference 2.27 (1.19–4.33)
PA: Year 1 after PA diagnosis	13 / 2,708	
Controls: Year 2 after GPRD start	52 / 34,353	Reference 0.95 (0.34–2.64)
PA: Year 2 after PA diagnosis	4 / 2,355	
Controls: Year 3 after GPRD start	45 / 28,728	Reference 4.31 (2.25–8.26)
PA: Year 3 after PA diagnosis	15 / 1,886	
Controls: Year 4 after GPRD start	36 / 23,859	Reference 3.28 (1.39–7.74)
PA: Year 4 after PA diagnosis	10 / 1,403	
Controls: >Year 5 after GPRD start	219 / 76,016	Reference 2.54 (1.69–3.83)
PA: >Year 5 after PA diagnosis	26 / 2,579	

Abbreviations: PA, pernicious anemia, CI, confidence interval; HR, hazard ratio

* Adjusted for sex and age in all years. In addition, additional covariates were included in the respective model if they resulted in >10% change in the age- and sex-adjusted model: smoking status in Year #1, alcoholism and current anxiolytic use in Year #4.