Original Investigation

Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B_{12} Deficiency

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IMPORTANCE Proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H_2RAs) suppress the production of gastric acid and thus may lead to malabsorption of vitamin B_{12}. However, few data exist regarding the associations between long-term exposure to these medications and vitamin B_{12} deficiency in large population-based studies.

OBJECTIVE To study the association between use of PPIs and H_2RAs and vitamin B_{12} deficiency in a community-based setting in the United States.

DESIGN, SETTING, AND PATIENTS We evaluated the association between vitamin B_{12} deficiency and prior use of acid-suppressing medication using a case-control study within the Kaiser Permanente Northern California population. We compared 25 956 patients having incident diagnoses of vitamin B_{12} deficiency between January 1997 and June 2011 with 184 199 patients without B_{12} deficiency. Exposures and outcomes were ascertained via electronic pharmacy, laboratory, and diagnostic databases.

MAIN OUTCOMES AND MEASURES Risk of vitamin B_{12} deficiency was estimated using odds ratios (ORs) from conditional logistic regression.

RESULTS Among patients with incident diagnoses of vitamin B_{12} deficiency, 3120 (12.0%) were dispensed a 2 or more years' supply of PPIs, 1087 (4.2%) were dispensed a 2 or more years' supply of H_2RAs (without any PPI use), and 21 749 (83.8%) had not received prescriptions for either PPIs or H_2RAs. Among patients without vitamin B_{12} deficiency, 13 210 (7.2%) were dispensed a 2 or more years' supply of PPIs, 5897 (3.2%) were dispensed a 2 or more years' supply of H_2RAs (without any PPI use), and 165 092 (89.6%) had not received prescriptions for either PPIs or H_2RAs. Both a 2 or more years' supply of PPIs (OR, 1.65 [95% CI, 1.58-1.73]) and a 2 or more years' supply of H_2RAs (OR, 1.25 [95% CI, 1.17-1.34]) were associated with an increased risk for vitamin B_{12} deficiency. Doses more than 1.5 PPI pills/d were more strongly associated with vitamin B_{12} deficiency (OR, 1.95 [95% CI, 1.77-2.15]) than were doses less than 0.75 pills/d (OR, 1.63 [95% CI, 1.48-1.78]; $P = .007$ for interaction).

CONCLUSIONS AND RELEVANCE Previous and current gastric acid inhibitor use was significantly associated with the presence of vitamin B_{12} deficiency. These findings should be considered when balancing the risks and benefits of using these medications.

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Vitamin B_{12} deficiency is relatively common, especially among older adults; it has potentially serious medical complications if undiagnosed. Left untreated, vitamin B_{12} deficiency can lead to dementia, neurologic damage, anemia, and other complications, which may be irreversible. According to data from the National Health and Nutrition Examination Survey, 3.2% of adults older than 50 years are estimated to have low serum vitamin B_{12} levels.[1] Other studies have reported prevalence rates of 5% to 15%, although these may be underestimates of the true prevalence in some population subgroups.[2,3] Thus, identifying modifiable risk factors for vitamin B_{12} deficiency is of significant public health importance.

Acid inhibitors are among the most commonly used pharmaceuticals in the United States. In 2012, 14.9 million patients received 157 million prescriptions for proton pump inhibitors (PPIs); thus, use of PPIs could theoretically increase the population's risk of vitamin B_{12} deficiency.[4] Gastric acid is required to cleave vitamin B_{12} from ingested dietary proteins for the essential vitamins to be absorbed, and it is produced by the same cells that produce intrinsic factor, a compound required for vitamin B_{12} absorption.[5] Thus, PPIs and histamine 2 receptor antagonists (H_2RAs), which suppress the production of gastric acid, may lead to malabsorption of vitamin B_{12}.

Studies examining the relationship of PPI use and vitamin B_{12} deficiency have focused primarily on small groups of elderly individuals and yielded inconsistent results. Although some studies suggested that acid suppressive medications are associated with lower vitamin B_{12} levels in older populations,[6-9] others found no association.[10-15] To our knowledge, no large population-based studies exist. Therefore, we performed a case-control study to evaluate the relationship between the use of acid-suppressing prescription medications and the risk of vitamin B_{12} deficiency within a large, community-based population.

Methods

Study Population

We conducted a nested case-control study within the Kaiser Permanente Northern California (KPNC) integrated healthcare system, which provides comprehensive inpatient and outpatient services for approximately 3.3 million members. The KPNC membership approximates the underlying census race/ethnicity and socioeconomic distributions of the Northern California region.[16] Prescription drug benefits are utilized by more than 90% of members. Databases electronically record dose, amount, directions for use, calculated days supply, and refills for all dispensed prescriptions; the performance of these databases is validated for both as-needed and daily medications.[17,18] Additional electronic databases include information on membership, medical diagnoses, and procedures performed. The study was approved by the KPNC institutional review board; the requirement for informed consent was waived.

Case Definition

Case patients were KPNC members who were at least 18 years of age, had at least 1 year of membership prior to the index date, and had an initial diagnosis of vitamin B_{12} deficiency between January 1997 and June 2011. The index date was the first date of diagnosis for vitamin B_{12} deficiency, or the first date of vitamin B_{12} supplement treatment, for case patients and matched controls. Vitamin B_{12} deficiency was defined as the presence of 1 of the following: the first diagnostic code for vitamin B_{12} deficiency, using *International Classification of Diseases, Ninth Revision* codes 281.0 (pernicious anemia), 281.1 (other vitamin B_{12} deficiency anemia), 266.2 (specified at KPNC as vitamin B_{12} deficiency), or specific text diagnoses of vitamin B_{12} deficiency in the problem list; an abnormally low value for serum vitamin B_{12}; or a new and at least 6-month supply of injectable vitamin B_{12} supplements. Sensitivity analyses were performed for the different case definitions.

Control Definition

For each case patient, up to 10 matched control patients (as available by matching criteria) were randomly selected from the KPNC membership using incidence density sampling; controls were chosen from among all eligible adult members who lacked a diagnosis of vitamin B_{12} deficiency at the time of the case diagnosis.

Controls were matched by sex, region of home facility, race/ethnicity, year of birth within 1 year of the matched case, and membership duration (rounded to year) within 1 year.

Exposure Status

Medication exposure status was determined using the KPNC pharmacy database and a priori definitions of prior medication use. The primary exposure definition used a "days supplied" variable that combined the number of pills dispensed with the instructions for use; for example, a prescription for 60 pills twice a day equaled a 30-day supply. The exposure duration was the interval between the first and last prescriptions plus the days supplied for the last prescription. We evaluated adherence and dose intensity using the "mean daily dose" (dispensed pills divided by exposure duration) and 3 dose categories: less than 0.75 pills/d, 0.75 to 1.49 pills/d, and 1.5 pills/d or more.

For the primary PPI analyses, exposed patients were defined as those who received at least a 2-year supply of PPIs prior to their index date; the unexposed (reference) group was defined as patients without current or prior prescriptions for either PPIs or H_2RAs. Exposure was further stratified by dose and duration. Because PPIs are more potent than H_2RAs, PPI-exposed patients may have also taken H_2RAs.

For the primary H_2RA analyses, exposed patients were defined as those who had received at least a 2-year supply of H_2RAs and did not have a current or prior prescription for PPIs.

Confounding

The potential for confounding was evaluated by considering conditions associated with vitamin B_{12} deficiency (ie, dementia, diabetes mellitus, thyroid disease, *Helicobacter pylori* infection, alcohol abuse, smoking, atrophic gastritis, and achlorhydria)[19-25] using *International Classification of Diseases, Ninth Revision* coding prior to the index date. We also evaluated whether expected positive associations were present for other medications known to be associated with vitamin B_{12} deficiency or with the treatment of associated conditions (ie, among persons receiving thyroid supplementation or metformin[26]).

The potential for confounding by health service utilization was also evaluated, given that patients who utilize medical services may have greater opportunities to be diagnosed with vitamin B_{12} deficiency and to receive a prescription for acid inhibitors, even if no causal association exists. Thus, we evaluated, as surrogates for use of care, common diagnostic codes not linked to B_{12} deficiency or acid-suppressing medications (ie, hypertension, arthritis, and use of screening tests such as a history of colon polyp). We also examined whether other commonly used medications were associated with vitamin B_{12} deficiency (ie, estrogen therapy, thiazide diuretics, angiotensin-converting enzymes, calcium channel blockers) and whether similar associations were found only among persons with gastroesophageal reflux disease (GERD), comparing patients having a GERD diagnosis who used PPIs with patients having a GERD diagnosis who had no recorded prescription use of acid-suppressing medications. Patients were considered to have been exposed to metformin if they had received at least a 180-day supply in the 500 days prior to the index date. For all other medications, patients were consid-

ered exposed if they had received 1 or more prescriptions prior to the index date.

We evaluated whether asymptomatic screening for vitamin B_{12} deficiency in the KPNC population was greater among persons taking acid-suppressing medications than among those not taking such medications. For this analysis, among all KPNC members older than 40 years with at least 2 years of membership, we identified persons who had (vs had not) received at least 1 prescription for a PPI and the proportion who subsequently received a laboratory test to measure vitamin B_{12} level in the years 2009 through March 2013.

Statistical Analysis

The study used standard analytic techniques for evaluating case-control studies and conditional logistic regression for evaluating multiple matched controls; the odds ratio (OR) was used as an estimate of the relative risk.[27-30] All primary definitions and modeling strategies were planned a priori. The "saturated" model contained all potential variables noted above. Confounding was evaluated by contrasting ORs between models with and without each potential confounder; the final model included factors that altered the OR by 10% or more.[27] Of all the conditions and medications evaluated, none met these criteria; thus, the final model was the bivariate model that included the outcome and the exposure. Effect modification was evaluated using cross-product terms in the logistic regression model and by evaluating stratum-specific ratios.[28] Significance was determined with a *P* value threshold of .05; tests for interaction (on the cross-product terms in the logistic regression), evaluations of differences between ORs, and the χ^2 test for trend used 2-sided testing. Comparable results were found for both the conditional and the unconditional logistic regression models; thus, all main results used conditional regression models. The prevalence estimate of vitamin B_{12} deficiency in the KPNC population was calculated among all persons older than 50 years who were KPNC members between January 2006 and December 2010. Analyses were performed using SAS version 9.3 (SAS Institute) and Stata version 10 (StataCorp).

Results

We identified 43 512 KPNC members with an incident diagnosis of vitamin B_{12} deficiency between January 1, 1997, and June 30, 2011. We excluded case patients lacking matched controls (n = 234), potential cases (n = 1751) and controls with diagnoses known to directly cause vitamin B_{12} deficiency, and potential cases (15 571) and controls who had taken PPIs or H_2RAs for less than 2 years. This resulted in 25 956 cases and 184 199 controls in the final analyses. Case patients were predominantly female (57.4%), 60 years or older (67.2%), and of non-Hispanic white race/ethnicity (68.4%) (**Table 1**). Among case patients, 3120 (12.0%) were dispensed a 2 or more years' supply of PPIs, 1087 (4.2%) were dispensed a 2 or more years' supply of H_2RAs (without any PPI use), and 21 749 (83.8%) had not received prescriptions for either PPIs or H_2RAs. Among control patients, 13 210 (7.2%) were dispensed a 2 or more years' supply of PPIs, 5897 (3.2%) were dispensed a 2 or more years' supply of H_2RAs (without any PPI use), and 165 092 (89.6%) had not received prescriptions for either PPIs or H_2RAs.

Table 1. Demographic Characteristics[a]

Characteristic	Patients, No. (%)	
	Cases (n = 25 956)	Controls (n = 184 199)
Sex		
Female	14 909 (57.4)	104 850 (56.9)
Male	11 047 (42.6)	79 349 (43.1)
Age at index date, y		
<30	747 (2.9)	6620 (3.6)
30-39	1598 (6.2)	13 100 (7.1)
40-49	2546 (9.8)	19 990 (10.9)
50-59	3611 (13.9)	27 290 (14.8)
60-69	4811 (18.5)	34 539 (18.7)
70-79	6426 (24.8)	43 755 (23.8)
80-89	5248 (20.2)	33 375 (18.1)
≥90	969 (3.7)	5530 (3.0)
Race/ethnicity		
White	17 755 (68.4)	127 787 (69.4)
Hispanic	2624 (10.1)	16 601 (9.0)
Black	1174 (4.5)	7934 (4.3)
Asian/Pacific Islander	1994 (7.7)	14 388 (7.8)
Multiracial	1256 (4.8)	7605 (4.1)
Other/unknown	1153 (4.5)	9884 (5.4)
Acid inhibitor use[b]		
≥2 y		
PPIs	3120 (12.0)	13 210 (7.2)
H_2RAs	1087 (4.2)	5897 (3.2)
None	21 749 (83.8)	165 092 (89.6)

Abbreviations: H_2RA, histamine 2 receptor antagonist; PPI, proton pump inhibitor.

[a] Case and control patients were matched for sex, age, duration of Kaiser Permanente Northern California membership, region, and race/ethnicity.

[b] Among users of acid suppression, H_2RA users had no PPI use; PPI users could also use H_2RAs. None designates patients with no PPI or H_2RA use.

Acid Inhibitor Use and Vitamin B_{12} Deficiency

A new diagnosis of vitamin B_{12} deficiency was more common among persons with a 2-year or greater supply of PPIs compared with nonusers (OR, 1.65 [95% CI, 1.58-1.73]). A total of 5746 case patients had received a 6 or more months' supply of B_{12} supplements; among these patients, 1962 had neither a recorded test result for B_{12} deficiency nor a recorded diagnosis of B_{12} deficiency. Similar positive associations were found using different case definitions, such as having both a low serum B_{12} level and a prescription for vitamin B_{12} supplements (OR, 1.50 [95% CI, 1.26-1.78]). Vitamin B_{12} deficiency was also associated with a 2 or more years' supply of H_2RAs (OR, 1.25 [95% CI, 1.17-1.34]).

Acid Inhibitor Dose and Vitamin B_{12} Deficiency

Among persons taking PPIs for 2 years or more, the highest mean daily dose was more strongly associated with vitamin B_{12} deficiency (≥1.5 PPI pills/d: OR, 1.95 [95% CI, 1.77-2.15]) than were lower doses (eg, <0.75 PPI pills/d: OR, 1.63 [95% CI, 1.48-1.78] and 0.75 to 1.49 PPI pills/d: OR, 1.55 [95% CI, 1.46-1.64];

Table 2. Associations Between 2 or More Years' Supply of Proton Pump Inhibitors (PPIs) and Vitamin B_{12} Deficiency, by Increasing Daily Dose and Cumulative Duration of Use[a]

Duration of PPI Use, y	Mean Daily PPI Dosage, Pills/d				Total PPI Users, No. (%)[b]	
	No PPI or H_2RA Use	<0.75	0.75-1.49	≥1.50	Cases (n = 24 854)	Controls (n = 178 226)
2-3.9						
Patients, No.[c]						
Cases	21 749	31	472	214	717 (2.8)	
Controls	165 092	153	2016	780		2949 (1.6)
OR (95% CI)	1 [Reference]	1.29 (0.86-1.95)	1.65 (1.49-1.84)	1.99 (1.70-2.33)		
4-5.9						
Patients, No.[c]						
Cases	21 749	156	471	144	771 (3.0)	
Controls	165 092	522	2121	562		3205 (1.7)
OR (95% CI)	1 [Reference]	2.03 (1.67-2.45)	1.56 (1.40-1.73)	1.80 (1.48-2.19)		
6-7.9						
Patients, No.[c]						
Cases	21 749	159	332	82	573 (2.2)	
Controls	165 092	711	1659	338		2708 (1.5)
OR (95% CI)	1 [Reference]	1.56 (1.30-1.87)	1.37 (1.21-1.55)	1.70 (1.32-2.19)		
8-9.9						
Patients, No.[c]						
Cases	21 749	158	268	68	494 (1.9)	
Controls	165 092	649	1146	220		2015 (1.1)
OR (95% CI)	1 [Reference]	1.62 (1.34-1.95)	1.62 (1.40-1.87)	2.06 (1.53-2.76)		
≥10						
Patients, No.[c]						
Cases	21 749	178	278	94	550 (2.1)	
Controls	165 092	795	1192	270		2257 (1.2)
OR (95% CI)	1 [Reference]	1.45 (1.22-1.73)	1.53 (1.33-1.77)	2.42 (1.87-3.13)		
All						
Patients, No.[c]						
Cases	21 749	682	1821	602	3105 (12.0)	
Controls	165 092	2830	8134	2170		13 134 (7.1)
OR (95% CI)	1 [Reference]	1.63 (1.48-1.78)	1.55 (1.46-1.64)	1.95 (1.77-2.15)		

Abbreviations: H_2RA, histamine 2 receptor antagonist; OR, odds ratio.

[a] Members in PPI user categories could also use H_2RAs. Table excludes 15 cases and 76 controls who had 2 or more years' supply of PPIs but less than 2 years' duration of use by calendar time (see Methods for definitions).

[b] Number of patients in each cumulative duration category. Numbers reported in column headings exclude some persons with less than 2 years of use; percentages derived from all cases (n = 25 956) and controls (n = 184 199).

[c] Case and control patients were individually matched for sex, age, duration of Kaiser Permanente Northern California membership, region, and race/ethnicity.

P = .007 for interaction for <0.75 vs ≥1.5 PPI pills/d) (**Table 2** and **Table 3**). There was a significant test for trend across all PPI dose categories, including nonusers (P < .001 for trend), although not among analyses confined only to different doses among users of PPIs, using the less than 0.75 pills/d category as the reference category (P = .22). Similar results were found for H_2RA use, with a significant test for trend across all categories of H_2RA use (P < .001 for trend), although not among only users of H_2RAs, using the less than 0.75 pills/d category as the reference category (P = .84 for trend).

Duration of Acid Inhibitor Use and Vitamin B_{12} Deficiency

There was a statistically significant increase in the association of vitamin B_{12} deficiency with longer durations of use among all PPI users (P < .001 for trend) (Tables 2 and 3), although this was primarily attributable to the difference between nonusers and users; no significant trend was found with increasing duration among analyses confined to patients with 2 or more years of PPI use (P = .38 for trend). There was also no trend in association with increasing duration of H_2RA use (P = .40 for trend).

Associations With Vitamin B_{12} Deficiency After Acid Inhibitor Discontinuation

The strength of the association between PPI use and vitamin B_{12} deficiency diminished after discontinuation of use (**Figure**). The association was stronger among recent users (≥2-year supply of PPIs and last prescription within 1 year prior to the index date) (OR, 1.80 [95% CI, 1.51-2.14]); in contrast, the association was weaker among persons whose most recent prescription was 2 to 2.9 years (OR, 1.43 [95% CI, 1.11-1.85]) and

Table 3. Associations Between 2 or More Years' Supply of Histamine 2 Receptor Antagonists (H_2RAs) and Vitamin B_{12} Deficiency, by Increasing Daily Dose and Cumulative Duration of Use[a]

Duration of H_2RA Use, y	Mean Daily H_2RA Dosage, Pills/d				Total H_2RA Users, No. (%)[b]	
	No PPI or H_2RA Use	<0.75	0.75-1.49	≥1.50	Cases (n = 22 812)	Controls (n = 170 910)
2-3.9						
Patients, No.[c]						
Cases	21 749	4	76	154	234 (0.9)	
Controls	165 092	31	530	839		1400 (0.8)
OR (95% CI)	1 [Reference]	0.87 (0.30-2.55)	0.95 (0.74-1.22)	1.33 (1.11-1.59)		
4-5.9						
Patients, No.[c]						
Cases	21 749	19	153	113	285 (1.1)	
Controls	165 092	94	736	606		1436 (0.8)
OR (95% CI)	1 [Reference]	1.58 (0.94-2.64)	1.36 (1.13-1.63)	1.32 (1.07-1.63)		
6-7.9						
Patients, No.[c]						
Cases	21 749	29	82	70	181 (0.7)	
Controls	165 092	188	514	395		1097 (0.6)
OR (95% CI)	1 [Reference]	0.95 (0.64-1.43)	1.10 (0.86-1.40)	1.26 (0.97-1.64)		
8-9.9						
Patients, No.[c]						
Cases	21 749	40	66	54	160 (0.6)	
Controls	165 092	219	348	235		802 (0.4)
OR (95% CI)	1 [Reference]	1.26 (0.89-1.80)	1.11 (0.84-1.46)	1.49 (1.09-2.03)		
≥10						
Patients, No.[c]						
Cases	21 749	68	79	56	203 (0.8)	
Controls	165 092	356	445	282		1083 (0.6)
OR (95% CI)	1 [Reference]	1.19 (0.90-1.57)	1.14 (0.89-1.47)	1.31 (0.96-1.77)		
All						
Patients, No.[c]						
Cases	21 749	160	456	447	1063 (4.1)	
Controls	165 092	888	2573	2357		5818 (3.2)
OR (95% CI)	1 [Reference]	1.19 (0.99-1.42)	1.16 (1.04-1.28)	1.37 (1.23-1.52)		

Abbreviation: OR, odds ratio.

[a] Members in H_2RA user categories did not use PPIs. Table excludes 24 cases and 79 controls who had 2 or more years' supply of H_2RAs but less than 2 years' duration of use by calendar time (see Methods for definitions).

[b] Number of patients in each cumulative duration category. Numbers reported in column headings exclude some persons with less than 2 years of use; percentages derived from all cases (n = 25 956) and controls (n = 184 199).

[c] Case and control patients were individually matched for sex, age, duration of Kaiser Permanente Northern California membership, region, and race/ethnicity.

3 or more years before the index date (OR, 1.38 [95% CI, 1.14-1.66]; P = .007 for trend).

Population Prevalence

The overall prevalence of vitamin B_{12} deficiency in our KPNC population was 2.3% for persons older than 50 years; using this as an estimate of the baseline population risk, an excess risk of 1.65 from the main model would provide a number needed to harm of 67 for 2 or more years of PPI use.

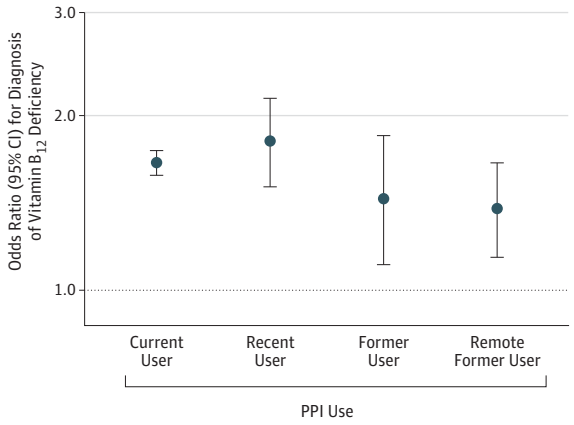
Presence of Other Risk Factors for Vitamin B_{12} Deficiency

The association between 2 or more years of PPI use and vitamin B_{12} deficiency was present among patients with no other risk factors for B_{12} deficiency (OR, 1.65 [95% CI, 1.42-1.91]) as well as among patients with 1 or more risk factors (OR, 1.50 [95% CI, 1.42-1.58]) (eTable in Supplement). The associations were comparable among persons with each risk factor and also comparable with the odds from our final model (OR, 1.65 [95% CI, 1.58-1.73]), with the exception of *H pylori* infection (absent: OR, 1.66 [95% CI, 1.58-1.74]; present: OR, 0.95 [95% CI, 0.49-1.83]; P < .001 for interaction) (eTable in Supplement).

Age, Sex, and Indication for Acid Inhibitor Treatment

The association between 2 or more years of PPI use and vitamin B_{12} deficiency differed by age (P < .001 for interaction); it was strongest among those younger than 30 years (OR, 8.12 [95% CI, 3.36-19.59]) and decreased with increasing age (OR, 1.04 [95% CI, 0.96-1.13] for ages 80 years or older, for example). The association was stronger among women (OR, 1.84 [95% CI, 1.74-1.95]) than men (OR, 1.43 [95% CI, 1.33-1.53];

Figure. Association Between a 2 or More Years' Supply of Proton Pump Inhibitors (PPIs) and a Diagnosis of Vitamin B_{12} Deficiency, Stratified by Time Since Most Recent Prescription



Patients, No.				
Cases	2697	190	79	154
Controls	11 458	668	363	721

Patients in the current user category received their last PPI prescription in the last year prior to the index date; those in the recent user category received their last PPI prescription 1 to 1.9 years prior to the index date; those in the former user category received their last PPI prescription 2 to 2.9 years prior to the index date; those in the remote former user category received their last PPI prescription 3 or more years prior to the index date.

$P < .001$ for interaction). There was no significant interaction by race/ethnicity ($P = .18$). An association was present among both persons with a GERD diagnosis (OR, 1.41 [95% CI, 1.25-1.59] for ≥2 years of PPI use vs no recorded use of acid-suppressing medications) and persons without a GERD diagnosis (OR, 1.70 [95% CI, 1.49-1.95] for ≥2 years of PPI use vs no recorded use of acid-suppressing medications).

Additional Analyses

The associations between vitamin B_{12} deficiency and other medications or medical conditions were generally in accordance with expected values (**Table 4**). For medications and conditions not known to be mechanistically linked with vitamin B_{12} deficiency, we found no significant association or only weak associations; for medications and conditions with known associations, the relationships were in the expected positive direction.

The associations between prescriptions for at least a 2-year supply of PPIs and B_{12} deficiency were similar among cases diagnosed in the years 1997-2003 (prior to PPIs being available over the counter; OR, 1.55 [95% CI, 1.34-1.80]) and among cases diagnosed in the years 2004 to 2011 (after PPIs also became available over the counter; OR, 1.67 [95% CI, 1.59-1.75]).

During the years 2009-2013, among all KPNC members older than 40 years with at least 2 years of membership, 26.8% of those who had received at least 1 PPI prescription also received a subsequent test for vitamin B_{12}, compared with 17.2% of persons who had not received a PPI prescription (unmatched by age, sex, and other factors); this difference decreased with matching by sex and age (eg, among men between the ages of 60 and 69 years, the proportions were 24.0% and 17.4%). Unlike the adjusted ORs, which used a matched design, these proportions do not account for other differences between these groups, such as duration of membership or comorbid conditions. A chart review of 20 randomly selected case patients who had been taking PPIs for 2 or more years to determine indications for B_{12} testing found that 25% had been tested for anemia, 20% for neuropathy, 15% for fatigue or symptoms of anemia, 15% for ataxia, and 15% for memory loss or psychiatric issues; 10% had no clear indication.

Discussion

In our study, use of acid-inhibiting medications for 2 or more years was associated with a subsequent new diagnosis of vitamin B_{12} deficiency. The magnitude of the association was stronger in women and younger age groups with more potent acid suppression (PPIs vs H_2RAs) and decreased after discontinuation of use. There was no significant trend with increasing duration of use and no strong evidence for confounding by utilization of medical care.

These findings extend those of prior small studies that evaluated acid inhibitor use and vitamin B_{12} deficiency. A case-control study of 53 patients with vitamin B_{12} deficiency in a geriatric primary care setting found that current use of PPIs/H_2RAs for 12 or more months was associated with vitamin B_{12} deficiency (OR, 4.45 [95% CI, 1.47-13.34]) but reported no association for past or short-term use.[7] In contrast, a cross-sectional study of 542 elderly patients found that prolonged PPI use was associated with decreased vitamin B_{12} levels, but prolonged H_2RA use was not.[8] These results differ from those of a Dutch study of 125 PPI users older than 65 years that reported no association between PPI use and vitamin B_{12} status, although the reference group consisted of partners of the users and the study had limited power.[12] Two other studies in children reported no association.[13,14] The discrepancies in findings may be explained by smaller sample sizes and differences in the populations studied (ie, elderly vs children).

Several findings in this study met Hill's criteria for a possible causal association between the use of acid-suppressing medications and vitamin B_{12} deficiency.[31] These included the strength of the association, with ORs of approximately 2 among patients with higher doses of exposure; temporality of the effect, with decreasing associations after discontinuation of acid inhibitor use; evidence of a dose response, with stronger associations found among patients taking the more potent PPI medications and weakening of the associations after medication discontinuation; plausibility, with a potential mechanism of action on the gastric parietal cells and a prior clinical trial that demonstrated decreased B_{12} absorption among persons taking omeprazole[9]; and consistency, with associations found for different types of acid inhibitors. Supplemental analyses suggest that the findings are not solely explained by health service utilization. For example, no similar strong associations were found with other commonly used medications, even though expected associations were found for medications and conditions with known associations with vitamin B_{12} deficiency. The overall association was also greater than that for other conditions with known associations with B_{12} deficiency, such as thy-

Table 4. Associations Between Other Diagnoses, Other Medication Use, and Vitamin B_{12} Deficiency

	No. (%)		
	Cases (n = 25 956)	Controls (n = 184 199)	OR (95% CI)[a]
Known associations with B_{12} deficiency			
Medications[b]			
Metformin	2677 (10.3)	7499 (4.1)	2.19 (2.06-2.33)
Thyroid supplementation	4791 (18.5)	20 975 (11.4)	1.36 (1.28-1.46)
Medical conditions[c]			
Achlorhydria	1 (0)	3 (0)	0.98 (0.10-9.82)
Alcohol abuse	4296 (16.6)	20 545 (11.2)	1.52 (1.46-1.58)
Atrophic gastritis	121 (0.5)	304 (0.2)	1.58 (1.25-1.99)
Dementia	3161 (12.2)	8732 (4.7)	2.82 (2.68-2.97)
Diabetes	6098 (23.5)	27 545 (15.0)	1.08 (1.04-1.13)
Helicobacter pylori infection	776 (3.0)	3256 (1.8)	1.15 (1.05-1.27)
Smoking	10 047 (38.7)	55 167 (30.0)	1.27 (1.23-1.31)
Thyroid disease	4893 (18.9)	20 850 (11.3)	1.29 (1.21-1.38)
No known associations with B_{12} deficiency			
Medications			
ACE inhibitors	9676 (37.3)	51 083 (27.7)	1.05 (1.01-1.09)
Calcium channel blockers	5827 (22.5)	31 236 (17.0)	1.03 (0.99-1.07)
Thiazide diuretics	6045 (23.3)	34 200 (18.6)	0.99 (0.95-1.03)
Medical conditions			
Arthritis	9391 (36.2)	50 736 (27.5)	1.26 (1.22-1.30)
Essential hypertension	14 650 (56.4)	82 796 (45.0)	1.28 (1.23-1.33)
Estrogen	5082 (19.6)	31 695 (17.2)	1.05 (1.01-1.10)
History of colon polyp	2030 (7.8)	11 535 (6.3)	1.08 (1.03-1.15)

Abbreviations: ACE, angiotensin-converting enzyme; OR, odds ratio.

[a] From saturated model, adjusted for use of other medications and risk factors.

[b] Except for metformin, medications are for any prescription prior to the index date (see Methods).

[c] Listed diagnoses are those associated with increased risk in the saturated regression model (see Methods for details). All listed diagnoses were included as risk factors in analyses of other risk factors for vitamin B_{12} deficiency.

roid disease.[21,32] The prevalence of diagnosed vitamin B_{12} deficiency in the KPNC population older than 50 years (in which not all people are tested) is 2.3%, which is comparable with the prevalence estimate of 3.2% among persons in the National Health and Nutrition Examination Survey older than 50 years, a sample in which all persons were tested.[1]

This study has several potential limitations. Spurious associations may be seen with variables related to the utilization of medical services, and case-control studies may not be able to completely control for such confounding. However, adjustment for other common medical conditions and restricting the analyses to patients with or without a diagnosis of GERD still demonstrated persistent positive associations, and no strong associations were found for other commonly used medications. Even adjustment for multiple conditions, including ones associated with B_{12} deficiency, which can lead to overmatching, decreased but did not eliminate the association. Although no guidelines recommend that patients taking acid inhibitors be screened for B_{12} deficiency, ascertainment bias is potentially a concern if patients taking acid-suppressing medications are more likely to be tested for B_{12} deficiency. We would expect this bias to influence the results primarily if patients taking medications were being screened at a higher rate for asymptomatic disease, leading to chance discovery, but not if the exposure actually caused symptomatic disease and patients subsequently received a diagnostic evaluation. Although the rate of testing was higher among PPI users in the general population, the formal analyses adjusted for many factors (eg, duration of membership and age) not accounted for by these crude estimates, and the reasons for testing among the cases appeared to be symptom driven: only 10% of the cases sampled had no symptomatic indication for vitamin B_{12} testing. Thus, cases appeared to be defined by symptom-driven testing rather than testing from asymptomatic screening.

We did not evaluate associations for short periods of use (<1 year), given that such use may be for acute medical conditions and hospitalizations, although even short-term PPI use has been suggested to decrease vitamin B_{12} absorption under experimental conditions.[9,11,33] The mean daily dose was calculated using the first and last prescription dates and may not accurately represent consistent long-term medication use, especially for persons with smaller prescriptions averaged over time. Misclassification of exposure status may influence the results. Even though KPNC members receive discounted prescriptions, some may take over-the-counter PPIs or H_2RAs not detected by the pharmacy databases; however, similar associations were seen even for earlier periods, and over-the-counter-use would be expected to decrease the strength of the association toward the null.

The strengths of this study include its large size, access to care for all members, up to 15 years of exposure data, the ascertainment of all recorded diagnoses of vitamin B_{12} deficiency arising within the study population (thereby minimizing referral bias), detailed electronic data for dispensed medication (eliminating recall bias), and the use of a control group that approximates the underlying general population of the region. The large study size permitted evaluation for small

intervals of use and for multiple potential confounders, including confounding by health service utilization.

Conclusion

This study found an association between the use of PPIs and H_2RAs for 2 or more years and a subsequent diagnosis of vitamin B_{12} deficiency. We cannot completely exclude residual confounding as an explanation for these findings, but, at minimum, the use of these medications identifies a population at higher risk of B_{12} deficiency, independent of additional risk factors. These findings do not recommend against acid suppression for persons with clear indications for treatment, but clinicians should exercise appropriate vigilance when prescribing these medications and use the lowest possible effective dose. These findings should inform discussions contrasting the known benefits with the possible risks of using these medications.

ARTICLE INFORMATION

Author Contributions: Dr Corley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lam, Corley.
Acquisition of data: Lam, Corley.
Analysis and interpretation of data: Lam, Schneider, Zhao, Corley.
Drafting of the manuscript: Lam, Schneider, Zhao, Corley.
Critical revision of the manuscript for important intellectual content: Schneider, Corley.
Statistical analysis: Lam, Zhao, Corley.
Obtained funding: Corley.
Administrative, technical, or material support: Schneider, Corley.
Study supervision: Schneider, Corley.

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REFERENCES

1. Evatt MLMP, Bobo JK, Kimmons J, Williams J. Why Vitamin B12 Deficiency Should Be on Your Radar Screen. Centers for Disease Control and Prevention website. http://www.cdc.gov/ncbddd/b12/index.html. Accessed July 18, 2012.

2. Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr*. 1994;60(1):2-11.

3. Pennypacker LC, Allen RH, Kelly JP, et al. High prevalence of cobalamin deficiency in elderly outpatients. *J Am Geriatr Soc*. 1992;40(12):1197-1204.

4. Declining Medicine Use and Costs: For Better or Worse? A Review of the Use of Medicines in the United States in 2012. IMS Health website. http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/2012%20U.S.%20Medicines%20Report/2012_U.S.Medicines_Report.pdf. 2013.

5. Toh BH, van Driel IR, Gleeson PA. Pernicious anemia. *N Engl J Med*. 1997;337(20):1441-1448.

6. Termanini B, Gibril F, Sutliff VE, et al. Effect of long-term gastric acid suppressive therapy on serum vitamin B_{12} levels in patients with Zollinger-Ellison syndrome. *Am J Med*. 1998;104(5):422-430.

7. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H_2 blocker or proton pump inhibitor use and risk of vitamin B_{12} deficiency in older adults. *J Clin Epidemiol*. 2004;57(4):422-428.

8. Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B_{12} status in older adults? *J Am Med Dir Assoc*. 2008;9(3):162-167.

9. Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B_{12}). *Ann Intern Med*. 1994;120(3):211-215.

10. Koop H, Bachem MG. Serum iron, ferritin, and vitamin B_{12} during prolonged omeprazole therapy. *J Clin Gastroenterol*. 1992;14(4):288-292.

11. Schenk BE, Festen HP, Kuipers EJ, Klinkenberg-Knol EC, Meuwissen SG. Effect of short- and long-term treatment with omeprazole on the absorption and serum levels of cobalamin. *Aliment Pharmacol Ther*. 1996;10(4):541-545.

12. den Elzen WP, Groeneveld Y, de Ruijter W, et al. Long-term use of proton pump inhibitors and vitamin B_{12} status in elderly individuals. *Aliment Pharmacol Ther*. 2008;27(6):491-497.

13. ter Heide H, Hendriks HJ, Heijmans H, et al. Are children with cystic fibrosis who are treated with a proton-pump inhibitor at risk for vitamin B(12) deficiency? *J Pediatr Gastroenterol Nutr*. 2001;33(3):342-345.

14. Tolia V, Boyer K. Long-term proton pump inhibitor use in children: a retrospective review of safety. *Dig Dis Sci*. 2008;53(2):385-393.

15. Hirschowitz BI, Worthington J, Mohnen J. Vitamin B_{12} deficiency in hypersecretors during long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther*. 2008;27(11):1110-1121.

16. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82(5):703-710.

17. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs. *Lancet*. 2005;365(9458):475-481.

18. Schatz M, Zeiger RS, Vollmer WM, et al. Validation of a beta-agonist long-term asthma control scale derived from computerized pharmacy data. *J Allergy Clin Immunol*. 2006;117(5):995-1000.

19. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med*. 1988;318(26):1720-1728.

20. Pflipsen MC, Oh RC, Saguil A, et al. The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes [published correction appears in *J Am Board Fam Med*. 2010;23(5):695]. *J Am Board Fam Med*. 2009;22(5):528-534.

21. Jabbar A, Yawar A, Waseem S, et al. Vitamin B_{12} deficiency common in primary hypothyroidism [published correction appears in *J Pak Med Assoc*. 2009;59(2):126]. *J Pak Med Assoc*. 2008;58(5):258-261.

22. Kaptan K, Beyan C, Ural AU, et al. *Helicobacter pylori*—is it a novel causative agent in vitamin B_{12} deficiency? *Arch Intern Med*. 2000;160(9):1349-1353.

23. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. *Am J Clin Nutr*. 1997;66(4):741-749.

24. Dastur DK, Quadros EV, Wadia NH, Desai MM, Bharucha EP. Effect of vegetarianism and smoking on vitamin B_{12}, thiocyanate, and folate levels in the blood of normal subjects. *Br Med J*. 1972;3(5821):260-263.

25. Laufer EM, Hartman TJ, Baer DJ, et al. Effects of moderate alcohol consumption on folate and vitamin B(12) status in postmenopausal women. *Eur J Clin Nutr*. 2004;58(11):1518-1524.

26. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B(12) deficiency in patients receiving metformin. *Arch Intern Med*. 2006;166(18):1975-1979.

27. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

28. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. 2nd ed. New York, NY: Wiley; 2000.

29. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research : Principles and Quantitative Methods*. Belmont, CA: Lifetime Learning Publications; 1982.

30. Breslow NE, Day NE. Statistical methods in cancer research: volume I—the analysis of case-control studies. *IARC Sci Publ*. 1980;(32):5-338.

31. Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295-300.

32. Ness-Abramof R, Nabriski DA, Braverman LE, et al. Prevalence and evaluation of B_{12} deficiency in patients with autoimmune thyroid disease. *Am J Med Sci*. 2006;332(3):119-122.

33. Saltzman JR, Kemp JA, Golner BB, et al. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin B_{12} absorption. *J Am Coll Nutr*. 1994;13(6):584-591.