Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B₁₂ Deficiency

Jameson R. Lam, MPH¹; Jennifer L. Schneider, MPH¹; Wei Zhao, MPH²; Douglas A. Corley, MD, PhD³

ABSTRACT

Importance Proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H₂RAs) suppress the production of gastric acid and thus may lead to malabsorption of vitamin B₁₂. However, few data exist regarding the associations between long-term exposure to these medications and vitamin B₁₂ deficiency in large population-based studies.

Objective To study the association between use of PPIs and H₂RAs and vitamin B₁₂ deficiency in a community-based setting in the United States.

Design, Setting, and Patients We evaluated the association between vitamin B₁₂ deficiency and prior use of acid-suppressing medication using a case-control study within the Kaiser Permanente Northern California population. We compared 25,936 patients having incident diagnoses of vitamin B₁₂ deficiency between January 1997 and June 2011 with 184,599 patients without B₁₂ deficiency. Exposures and outcomes were ascertained via electronic pharmacy, laboratory, and diagnostic databases.

Main Outcomes and Measures Risk of vitamin B₁₂ deficiency was estimated using odds ratios (ORs) from conditional logistic regression.

Results Among patients with incident diagnoses of vitamin B₁₂ deficiency, 3,120 (12.0%) were dispensed a 2 or more years’ supply of PPIs, 1087 (4.2%) were dispensed a 2 or more years’ supply of H₂RAs (without any PPI use), and 2,109 (83.8%) had not received prescriptions for either PPIs or H₂RAs. Among patients without vitamin B₁₂ deficiency, 13,210 (7.2%) were dispensed a 2 or more years’ supply of PPIs, 5,897 (3.2%) were dispensed a 2 or more years’ supply of H₂RAs (without any PPI use), and 165,092 (89.6%) had not received prescriptions for either PPIs or H₂RAs. 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 H₂RAs (OR, 1.25 [95% CI, 1.17-1.34]) were associated with an increased risk for vitamin B₁₂ deficiency. Doses more than 1.5 PPI pills/d were more strongly associated with vitamin B₁₂ 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 B₁₂ deficiency. These findings should be considered when balancing the risks and benefits of using these medications.

Vitamin B₁₂ deficiency is relatively common, especially among older adults; it has potentially serious medical complications if undiagnosed. Left untreated, vitamin B₁₂ 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 B₁₂ levels. Other studies have reported prevalence rates of 5% to 15%, although these may be underestimates of the true prevalence in some population subgroups. Thus, identifying modifiable risk factors for vitamin B₁₂ 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 B₁₂ deficiency. Gastric acid is required to...
clease 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. 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, others found no association. 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**

**ABSTRACT | METHODS | RESULTS | DISCUSSION | CONCLUSION | ARTICLE INFORMATION | REFERENCES**

**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. 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. 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), 286.2 (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$_2$RAs. Exposures were stratified by dose and duration. Because PPIs are more potent than H$_2$RAs, PPI-exposed patients may have also taken H$_2$RAs.

For the primary H$_2$RA analyses, exposed patients were defined as those who had received at least a 2-year supply of H$_2$RAs 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) using International Classification of Diseases, Ninth Revision coding prior to the index date. We also evaluated whether expected positive associations were

<table>
<thead>
<tr>
<th>Adverse Drug Effects</th>
<th>Drug Therapy</th>
<th>Gastroenterology</th>
<th>Gastroesophageal Reflux Disease</th>
<th>Malnutrition</th>
</tr>
</thead>
</table>

**PubMed Articles**

[Acid inhibition leads to vitamin b12 deficiency]. Med Monatsschr Pharm 2014;37(5):190-1.

[Acid inhibition leads to vitamin b12 deficiency]. MMW Fortschr Med 2014;156(5):34.

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Results provided by:
present for other medications known to be associated with vitamin B<sub>12</sub> deficiency or with the treatment of associated conditions (ie, among persons receiving thyroid supplementation or metformin<sup>26</sup>).

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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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 considered exposed if they had received 1 or more prescriptions prior to the index date.

We evaluated whether asymptomatic screening for vitamin B<sub>12</sub> 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<sub>12</sub> 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.<sup>27-30</sup> 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.<sup>27</sup> 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.<sup>28</sup> 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<sup>2</sup> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> deficiency, and potential cases (15,571) and controls who had taken PPIs or H<sub>2</sub>RAs 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, 3,120 (12.0%) were dispensed a 2 or more years’ supply of PPIs, 10,874 (4.2%) were dispensed a 2 or more years’ supply of H<sub>2</sub>RAs (without any PPI use), and 184,199 (89.6%) had not received prescriptions for either PPIs or H<sub>2</sub>RAs. Among control patients, 13,210 (7.2%) were dispensed a 2 or more years’ supply of PPIs, 5,587 (3.2%) were dispensed a 2 or more years’ supply of H<sub>2</sub>RAs (without any PPI use), and 165,092 (89.6%) had not received prescriptions for either PPIs or H<sub>2</sub>RAs.

<table>
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<th>Table 1. Demographic Characteristics&lt;sup&gt;a&lt;/sup&gt;</th>
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Acid Inhibitor Use and Vitamin B₁₂ Deficiency

A new diagnosis of vitamin B₁₂ 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 B₁₂ supplements; among these patients, 1962 had neither a recorded test result for B₁₂ deficiency nor a recorded diagnosis of B₁₂ deficiency. Similar positive associations were found using different case definitions, such as having both a low serum B₁₂ level and a prescription for vitamin B₁₂ supplements (OR, 1.50 [95% CI, 1.26-1.78]). Vitamin B₁₂ deficiency was also associated with a 2 or more years' supply of H₂RAs (OR, 1.25 [95% CI, 1.17-1.34]).

Acid Inhibitor Dose and Vitamin B₁₂ Deficiency

Among persons taking PPIs for 2 years or more, the highest mean daily dose was more strongly associated with vitamin B₁₂ 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]; 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 H₂RA use, with a significant test for trend across all categories of H₂RA use (P < .001 for trend), although not among only users of H₂RAs, using the less than 0.75 pills/d category as the reference category (P = .84 for trend).

Table 2. Associations Between 2 or More Years’ Supply of Proton Pump Inhibitors (PPIs) and Vitamin B₁₂ Deficiency, by Increasing Daily Dose and Cumulative Duration of Use

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Cumulative Duration of Use</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.75 pills/d</td>
<td>2 or more years' supply</td>
<td>1.55</td>
<td>1.46-1.64</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0.75 to 1.49 pills/d</td>
<td>2 or more years' supply</td>
<td>1.63</td>
<td>1.48-1.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥1.5 pills/d</td>
<td>2 or more years' supply</td>
<td>1.95</td>
<td>1.77-2.15</td>
<td>&lt;.001</td>
</tr>
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</table>

There was a statistically significant increase in the association of vitamin B₁₂ 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$_2$RA 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 3 or more years before the index date (OR, 1.38 [95% CI, 1.14-1.66]; $P = .007$ for trend).

**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 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.

**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]; $P < .001$ 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, 1.49-1.93] 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.

**Table 4.** Associations Between Other Diagnoses, Other Medication Use, and Vitamin B$_{12}$ Deficiency

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 B₁₂, compared with 17.2% of persons who had not received a PPI prescription (unmatched by age, with ORs of approximately 2 among patients with higher doses of exposure; temporality of the effect, with B₁₂ deficiency, such as thyroid disease. The prevalence of diagnosed vitamin B₁₂ deficiency in the years 1997-2003 (prior to PPIs being available over the counter; OR, 1.55 [95% CI, 1.34-1.80]) but reported no association for past or short-term use. In contrast, a cross-sectional study of 542 elderly patients found that prolonged PPI use was associated with decreased vitamin B₁₂ levels, but prolonged H₂RA use was not. 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 B₁₂ status, although the reference group consisted of partners of the users and the study had limited power. Two other studies in children reported no association. 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 B₁₂ deficiency. 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 B₁₂ absorption among persons taking omeprazole; 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 B₁₂ deficiency. The overall association was also greater than that for other conditions with known associations with B₁₂ deficiency, such as thyroid disease. The prevalence of diagnosed vitamin B₁₂ 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.

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 B₁₂ deficiency, which can lead to overlapping, decreased but did not eliminate the association. Although no guidelines recommend that patients taking acid inhibitors be screened for B₁₂ deficiency, ascertainment bias is potentially a concern if patients taking acid-suppressing medications are more likely to be tested for B₁₂ 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 B₁₂ 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 B₁₂ absorption under experimental conditions. 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 H₂RAs 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 B₁₂ 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 H₂RAs for 2 or more years and a subsequent diagnosis of vitamin B₁₂ 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 B₁₂ 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

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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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