Lack of Association between Out-of-Hospital Use of Proton Pump Inhibitors and Hypomagnesemia at Hospital Admission: A Nested Case-Control Study

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Ioannis Koulouridis

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Table of Contents

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AUTHORS:
Ioannis Koulouridis, MD [1, 2]
Mansour Alfayez, MD [1, 2]
Hocine Tighiouart, MS [3]
Nicolaos E. Madias, MD, FASN [1, 2]
David M. Kent, MD, MSc [2, 3]
Jessica K. Paulus, ScD [3, 4]
Bertrand L. Jaber, MD, MS [1, 2]

ADDRESS FOR CORRESPONDENCE:
Bertrand L. Jaber, MD, MS
St. Elizabeth's Medical Center
736 Cambridge Street, Boston, MA 02135
Phone: (617) 562-7830
Facsimile: (617) 562-7797
E-mail: bertrand.jaber@steward.org

Affiliations
[1] Department of Medicine, Division of Nephrology, Kidney and Dialysis Research Laboratory, St. Elizabeth's Medical Center, Boston, MA
[2] Department of Medicine, Tufts University School of Medicine, Boston, MA
[3] Biostatistics Research Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University, Boston, MA
[4] Department of Epidemiology, Harvard School of Public Health, Boston, MA

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ABSTRACT

Background: Case series suggest that chronic use of proton pump inhibitors (PPIs) is associated with hypomagnesemia. Current literature lacks systematically collected data linking use of PPIs to hypomagnesemia. This study examines whether the presence of hypomagnesemia at time of hospital admission is associated with use of PPIs.

Study Design: Exact age and sex matched nested case-control study of 402 adult cases of hypomagnesemia at time of hospital admission, sex- and age-matched to 402 controls.

Setting and Participants: Data derived from abstracts of hospital discharges linked to the hospital's electronic laboratory database. Cases consisted of patients with hypomagnesemia (<1.4 mEq/L) at time of hospital admission. Control subjects consisted of patients with normal serum magnesium level (1.4-2.0 mEq/L) at time of hospital admission. For each patient, we included the first available hospitalization documenting ICD-9-CM diagnosis code for disorders of the esophagus, stomach and duodenum.

Predictor and Outcome: PPI use before hospitalization was identified in the hospital record. When possible, omeprazole equivalent dose was calculated. Conditional logistic regression was performed to examine the association of PPI use with hypomagnesemia. Adjustment variables included the Charlson-Deyo comorbidity index, diabetes, use of thiazide diuretics, estimated glomerular filtration rate (eGFR), and presence of gastro-esophageal reflux.

Results: PPI use was not associated with hypomagnesemia (adjusted odds ratio [OR] 0.82; 95% CI 0.61, 1.11). Neither PPI type nor omeprazole equivalent daily dose was associated with hypomagnesemia. No significant association was shown in adjusted sensitivity analyses of PPI use restricted to patients with esophageal disorders (OR 1.00; 95% CI 0.69, 1.45), severe hypomagnesemia (≤1.0 mEq/L) (OR 0.78; 95% CI 0.13, 4.61), or eGFR>60 ml/min/1.73 m^2 (OR 0.84; 95% CI 0.53, 1.34).

Limitations: Confounding and ascertainment bias of PPI use; inability to ascertain length of PPI use; and study sample restricted to hospitalized patients.

Conclusions: In a hospital-based adult population, use of PPI was not associated with hypomagnesemia at hospital admission.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most widely used drugs for the treatment of gastro-esophageal reflux disease (GERD), peptic ulcer disease, and conditions associated with increased gastric acid secretion. More prolonged therapy is required for adequate symptom control in patients with GERD [1]. While optimal duration of therapy is 4 and 8 weeks for acute gastric and duodenal ulcer, respectively [2], the Food and Drug Administration (FDA) advises that no more than three 14-day courses of PPI therapy be used in one year [3]. The more prolonged use of PPIs occurs in the elderly and in those taking non-steroidal anti-inflammatory drugs [4]. In 2003, PPIs became available over-the-counter in the U.S. [5], further increasing their widespread use, and by 2009, they constituted the third highest drug class in sales after antipsychotics and lipid lowering drugs [6].

Proton pump inhibitors are generally considered safe drugs with rare side effects, including diarrhea, vitamin B_{12} and iron deficiency, *Clostridium difficile* colitis, and the recent description of several cases of hypomagnesemia [7]. Indeed, 31 cases of hypomagnesemia associated with the use of PPIs have been reported to date [8-22]. In these cases, a common characteristic was the chronic use of PPIs of more than one-year duration and the presence of severe hypomagnesemia (Supplemental Table 1). Fifteen additional cases have been reported through the Adverse Event Reporting System of the FDA, which recently recognized hypomagnesemia related to the chronic use of PPI with a safety announcement [23,24]. This safety announcement is based only on a series of case reports, underlining the lack of systematically collected data linking use of PPIs with hypomagnesemia.

The aim of this case-control study was to examine whether the presence of hypomagnesemia at the time of hospital admission is associated with out-of-hospital use of PPIs. We tested this hypothesis in a large cohort of hospitalized adults.

METHODS

Data Source

The dataset used for this study contained fully-de-identified hospital discharges at an acute care facility (Saint Elizabeth's Medical Center, Boston, MA) over a 7-year period (October 1, 2000 to September 30, 2007). Institutional Review Board approval was obtained. Discharge abstracts provided information on patient's age, sex, race/ethnicity, dates of admission and discharge, hospital service type (medical, surgical, and other), up to 15 International Classification of Diseases-9th Edition-Clinical Modification (ICD-9-CM) diagnosis codes, and procedural codes. Each discharge abstract was linked to the hospital's electronic laboratory database.

Study Design

This was a single-center, nested case-control study with a 1:1 matched ratio. The source population consisted of all consecutive patients hospitalized at an acute care facility irrespective of diagnosis and concomitant comorbidities. Cases consisted of patients with a low serum magnesium level at time of hospital admission or the following day, defined as <1.4 mEq/L (<1.7 mg/dL), in accordance with the clinical laboratory's lower cut-off value. Control subjects were sex- and age-(±1 year) matched to cases and consisted of patients with a normal serum magnesium level of 1.4-2.0 mEq/L (1.7-2.5 mg/dL) at time of hospital admission or the following day. We specifically excluded control subjects with a high serum magnesium level of >2.0 mEq/L (>2.5 mg/dL) to minimize the potential influence on magnesium levels of patient-related factors that can be associated with hypermagnesemia.

Inclusion and Exclusion Criteria

Computerized random chart selection was conducted using simple random sampling and assessment of inclusion and exclusion criteria was performed electronically using the ICD-9-CM diagnosis codes. We restricted our population to the first available hospitalization of adults (age ≥ 18 years) to medical services, with a documented ICD-9-CM diagnosis code for GERD, esophagitis, Barrett's esophagus, peptic ulcer disease, gastrinoma, upper gastrointestinal bleeding, gastritis, duodenitis, mucositis, or dyspepsia (Supplemental Table 2). This restriction of diagnoses targeted our population towards patients with disorders of the upper gastrointestinal tract, a population that is more likely to use PPIs chronically. The restriction to the first available hospitalization of each patient assured that most of the cases of hypomagnesemia were newly diagnosed incident cases.

Coexisting conditions that may confound the association of low serum magnesium levels with PPI use were avoided by excluding patients with ICD-9-CM diagnosis codes for acute diarrheal syndromes, enteritis, enterocolitis, colitis, ulcerative colitis, Crohn's disease, regional enteritis, small bowel bypass surgery, alcoholism, pancreatitis, primary hyperparathyroidism, primary hyperaldosteronism, cardiopulmonary bypass, and kidney transplantation (Supplemental Table 2).

Ascertainment and Validation of Out-of-Hospital PPI Use

Out-of-hospital use of PPIs was ascertained by reviewing admission notes and discharge summaries documented in the electronic medical record (*method 1*) using a structured data collection form. If the hospital admission medication list was not present in these source documents, the nursing electronic medication administration record (*method 2*) for the corresponding hospitalization was reviewed. In this case, PPI use was presumed only

if the medication was prescribed during the total length of the hospitalization *and* at time of hospital discharge.

We determined the diagnostic accuracy of the two PPI use ascertainment methods (index tests) in a subgroup of our participants. To that end, we randomly selected 239 discharges (97 cases and 142 control subjects) and conducted a manual chart review (gold standard test). This procedure allowed us to calculate the sensitivity and specificity of the two methods employed to ascertain PPI use.

Using a dose conversion factor, a daily omeprazole equivalent dose was also calculated whenever the daily dose of the PPI was documented. In brief, a 20 mg oral dose of omeprazole was considered to have equivalent therapeutic efficacy to 20 mg of esomeprazole, 30 mg of lansoprazole, 40 mg of pantoprazole, and 20 mg of rabeprazole [25, 26].

Description of Covariates

According to current literature [27, 28] and clinical judgment, the following covariates were considered: age, sex, race/ethnicity, presence of diabetes mellitus, the Charlson-Deyo comorbidity index and its individual components, GERD and other disorders of the upper gastrointestinal tract, out-of-hospital use of drugs that may affect serum magnesium level (diuretics, aminoglycosides, anti-fungal, chemotherapeutic, immunosuppressive, and anti-protozoal drugs), and selected laboratory variables obtained at time of hospital admission (serum creatinine, calcium, and albumin). The Charlson-Deyo comorbidity index incorporates a history of comorbidities, using ICD-9-CM diagnosis codes [29, 30]. A Charlson-Deyo score between 0 and ≥ 3 was generated, with increasing numerical value reflecting greater comorbidity. Presence of diabetes and disorders of upper gastrointestinal tract were ascertained using an expanded list of ICD-9-CM diagnosis codes (Supplemental Table 2). If a laboratory variable was missing at time of hospital admission, the value measured within the

first day of hospitalization was used. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [31]. The use of medications at time of hospital admission was also ascertained according to the aforementioned method and included use of diuretics, aminoglycosides, and anti-fungal, chemotherapeutic, immunosuppressive, and anti-protozoal drugs.

Statistical Analysis

Continuous variables were described as mean (standard deviation) or median (25^{th} and 75^{th} percentile), and categorical variables as count (percentage). For the univariate analysis exploring the association of PPI use with hypomagnesemia, an *a priori* sample size calculation was performed to detect an odds ratio of 1.50 in exposed relative to unexposed subjects, with a power of 80% and a type-I error of 0.05, resulting in 414 pairs. We found that with 402 pairs, the study has adequate power to detect an odds ratio of 1.52.

Cases and controls comparisons were conducted using McNemar's test (for binary variables), paired t-test (for normally distributed continuous variables) and Wilcoxon signed-rank test (for non-normally distributed continuous variables). Categorical variables with more than 2 levels were compared using conditional logistic regression with and without the variable of interest and the likelihood ratio test was used.

Conditional logistic regression analyses were performed to examine the association of low serum magnesium level with out-of-hospital use of PPIs. Based on current literature as well as on analysis of differences between cases and controls, pre-specified adjustment variables included the Charlson-Deyo comorbidity index (0, 1, 2, ≥3), diabetes (yes/no), GERD (yes/no), out-of-hospital use of diuretics (yes/no for each diuretic type) and eGFR ($ml/min/1.73m^2$) at time of hospital admission. The results are displayed as odds ratio (OR) with 95% confidence interval (CI). Additional multivariable conditional logistic regression

analyses were performed to examine the association of low serum magnesium level with type of PPI as well as the daily omeprazole equivalent dose.

Several sensitivity analyses were conducted to explore the robustness of the findings including the removal of influential points (identified using DFBETAS and standardized DFBETAS), the restriction to cases with severe hypomagnesemia (≤1.0 mEq/L or ≤1.2 mg/dL), cases with esophageal disorders (including GERD), and cases with preserved kidney function (eGFR > 60 ml/min/1.73 m^2). Multivariable linear regression analysis was also used to examine the association of the serum magnesium level with out-of-hospital PPI use.

All analyses were conducted using R system software [32] Version 2.14.0. All P values were two tailed and considered to be statistically significant at the 0.05 level.

RESULTS

Derivation of the Analytical Dataset

A flow diagram describing the derivation of the analytical dataset is depicted in Figure 1. In brief, during the 7-year study period, there were a total of 65,533 hospitalizations, for 34,180 patients. After applying the exclusion criteria, 414 cases and 2,832 potential control subjects were identified. Using the MatchIt R package [33], we were able to identify exact sex and age controls for each case using a 1:1 ratio. Sufficient data on medication use at time of hospitalization were available for 402 pairs (804 patients), which comprised the final analytic dataset.

Population Characteristics

Table 1 displays the characteristics of the study participants. Cases and control subjects were adequately matched in age and sex. Mean age was 70 years and 40% of patients were men. Comorbidities were more prevalent in cases compared to controls, as evidenced by a higher Charlson-Deyo comorbidity index scores (p = 0.037), and a higher prevalence of diabetes (34.6% vs. 26.4%, p = 0.012). Cases had a higher prevalence of out-of-hospital thiazide diuretic use and lower serum calcium levels compared to controls. Although the prevalence of esophageal and gastro-duodenal disorders was not different between the 2 groups, GERD was unexpectedly more prevalent in controls as compared to cases (80.1% *vs.* 72.9%, p = 0.025).

Diagnostic Performance of PPI Use Ascertainment Methods

The diagnostic performance of *method 1* to ascertain use of PPIs (review of admission notes and discharge summaries in the electronic medical record) was better than that of *method 2* (review of nursing electronic medication record). Using manual chart review of 239 hospitalizations as the gold standard, sensitivity and specificity was 91.1% (95% CI 82.6, 96.4) and 96.0% (95% CI 86.3, 99.5) for *method 1*, and 84.5% (95% CI 72.6, 92.7) and 46.2% (95% CI 32.2, 60.5) for *method 2*, respectively. Positive and negative predictive value was 97.3% (95% CI 90.6, 99.7) and 87.3% (95% CI 75.5, 94.7) for *method 1*, and 63.6% (95% CI 51.9, 74.3) and 72.7% (95% CI 54.5, 86.7) for *method 2*, respectively.

Primary Analyses

The results of the conditional logistic regression analyses are shown in Table 2. In the unadjusted analysis and following adjustment for the Charlson-Deyo comorbidity index, presence of diabetes, GERD, diuretic use, and eGFR, out-of-hospital PPI use was not associated with higher odds for low serum magnesium levels at time of hospital admission

(adjusted OR 0.82; 95% CI 0.61, 1.11; p = 0.193). The results were also not significant for type of PPI use (global p = 0.129) as well as the omeprazole equivalent daily dose (adjusted OR 0.98; 95% CI 0.88, 1.10; p = 0.781).

Sensitivity Analyses

Results of the sensitivity analyses are displayed in Table 2. In brief, there was no association between PPI use and low serum magnesium levels in sensitivity analyses restricted to case-control pairs where ascertainment of PPI use was based on *method 1* that had better diagnostic performance, patients with severe hypomagnesemia, those with preserved kidney function, or esophageal disorders. Although out-of-hospital PPI use was associated with a 1.16 higher adjusted odds for low serum magnesium levels in an analysis restricted to patients with GERD, this association did not reach statistical significance (OR 1.16; 95% CI 0.76, 1.76).

Finally, using multivariable linear regression analysis, out-of-hospital PPI use was not associated with serum magnesium levels (β coefficient = 0.019; 95% CI -0.005, 0.043; p value = 0.432).

DISCUSSION

In the present nested case-control study of hospitalized adults on medical services, we find that out-of-hospital use of PPIs among patients with a disorder of the upper gastrointestinal tract involving the esophagus, stomach or duodenum is not associated with a low serum magnesium level at time of hospital admission. Our results remained unchanged after taking into consideration the type or the dose of the prescribed PPI. We defined

hypomagnesemia in accordance with the hospital's clinical laboratory serum magnesium lower cut-off value of 1.4 mEq/L. The cases reported in the literature (Supplemental Table 1) presented with lower serum magnesium levels with the highest value being at 0.9 mEq/L [18]. When we restricted our analysis to cases with serum magnesium levels of less than 1 mEq/L, we did not find any association between PPI use and low serum magnesium level. On linear regression analysis, after combining the cases and controls into one cohort, we were also unable to decipher any association between low serum magnesium levels and PPI use.

Although not statistically significant, our univariate analysis showed unexpectedly a tendency for a protective effect of PPI use against low serum magnesium levels, with observed odds ratios of less than 1.0. A possible explanation might be the bias inserted by an unanticipated higher prevalence rate of GERD in the control group. Although GERD has not been associated with low serum magnesium levels, its presence might be associated with a higher prevalence of chronic PPI users [1], thus influencing decisions upon prescription of these agents and introducing confounding by indication bias. To address this potential bias and provide internal validity to our findings, we adjusted our multivariate analysis for GERD and, additionally, performed sensitivity analyses restricted to patients with esophageal disorders or purely GERD. Although none of these analyses demonstrated an association between PPI use and hypomagnesemia, the odds ratio was greater than 1.0. Indeed, in the analysis of patients with GERD only, PPI use was associated with 1.16 higher odds for low serum magnesium level, but this did not reach statistical significance.

The potential mechanism of the alleged PPI-induced hypomagnesemia is elusive, but appears to be associated with chronic use of PPIs [17, 19]. The reported rarity of this association coupled with our inability to confirm such an association in a hospital-based patient population point to more uncertainties regarding this potential drug-related adverse event. Since the urinary excretion of magnesium has been reported to be consistently low in the

published case reports [8, 12, 17, 18], it is more likely that the putative cause is magnesium loss via the gastrointestinal system. In several reports, treatment with high-dose oral magnesium supplements was only partially effective, suggesting impaired intestinal absorption of magnesium [10, 15]. It has been speculated that PPIs might affect the function of the Transient Receptor Potential Melastatin-6 ($TRPM_6$) channel in the active transport pathway [10, 18] but confirmative studies are needed. $TRPM_6$ is responsible for the absorption of magnesium along the entire gastrointestinal tract and in the kidney [34].

Concomitant use of antacids, which often contain magnesium, with PPIs is not contraindicated [35] and sometimes necessary [1]. Therefore, the potential deleterious effect of PPI on serum magnesium level in patients with impaired kidney function might be confounded by the concomitant oral administration of magnesium-containing antacids, which would attenuate a decline in serum magnesium due to impaired GFR [17]. Our sensitivity analysis restricted to patients with eGFR > 60 ml/min/1.73m^2 attempted to address the confounding effect of impaired renal function, but yet found no association between PPI use and low serum magnesium. Moreover, by excluding patients with a high serum magnesium level of >2.0 mEq/L (>2.5 mg/dL), we further minimized the potential influence of impaired renal function on elevating serum magnesium levels, which might mask potential associations between PPI use and low magnesium levels.

Although PPI-associated hypomagnesemia was initially observed with omeprazole, it has also been described with other PPI compounds (Supplemental Table 1) [8, 10, 15, 17]. This finding justifies our approach to analyze PPI use in general. This potential drug-related adverse effect has been described as “non–dose related” [17], and we failed to demonstrate an association between the omeprazole equivalent daily dose and serum magnesium level.

Strengths and Limitations

Our study is the first to formally explore a potential association between hypomagnesemia and use of PPIs. Our results were consistent, irrespective of the statistical method used. Since the electronic chart review was conducted after the selection of cases and controls, we ensured that control subjects were sampled independently of exposure status. During the spanning period of the hospitalizations, a possible association between PPI use and hypomagnesemia had not been formally recognized in the literature and therefore prescription of these drugs was not influenced thereby minimizing confounding by indication bias.

The most difficult undertaking was the elimination of the effect of potential factors that confound the association of PPI use with hypomagnesemia. Matching and multivariable analyses taking into account the most important confounders of the association of PPI use with hypomagnesemia were used to minimize confounding. Selection bias might be present since the measurement of magnesium levels is not performed in patients unless there is a specific indication. There is no indication that this bias should be differential between cases and controls.

Non-differential exposure misclassification of the exposure variable is an important limitation, as out-of-hospital use of PPIs was conducted through review of electronic records, driving our results towards the null. The poor performance of *method 2* is indicative of this potential bias. Our restriction to patients ascertained using *method 1* as a sensitivity analysis was an attempt to account for this limitation.

In addition, we were unable to ascertain duration of PPI therapy. Since PPI-associated hypomagnesemia has been described in long-term users, ranging from 1 to 13 years (Supplemental Table 1), in an attempt to limit the study population to patients most likely to be *chronic* users of PPIs, we restricted the analysis to patients with disorders of the upper gastrointestinal tract, as a proxy for chronic use of these drugs. This choice also enabled us to

adequately power our study while keeping the sample size within a feasible limit because our sample was enriched with more PPI users. These imposed criteria for the derivation of the study population likely limit the external validity of our results.

Our dataset was derived from a single center and was restricted to hospitalized patients; therefore, it may not be representative of a broader ambulatory-based population that may use PPIs. To minimize this bias, our analysis was restricted to serum magnesium levels measured on day 1 or day 2 of hospitalization and not during the entire hospitalization. Also, we restricted our analysis to the first hospitalization of all patients, assuring independence between the pairs.

Clinical Implications

Magnesium loss in PPI users should be considered in the differential diagnosis of hypomagnesemia, but not as a highly likely cause. The risk of this potential side effect should not drive clinical decision against the use of these drugs unless the patient has a history of PPI-induced hypomagnesemia.

Conclusion

In a hospital-based adult population, out-of-hospital use of PPI is not associated with presence of low serum magnesium levels at time of hospital admission. Further studies with information on cumulative exposure and duration of PPI use are needed to address this potential medication-related issue. A cohort approach recruiting patients with GERD would avoid confounding by indication bias, ascertaining in parallel the exact induction time between PPI exposure and hypomagnesemia.

AUTHORS' CONTRIBUTIONS

Conception and design: I. Koulouridis, B.L. Jaber, Nicolaos E. Madias

Analysis and interpretation of the data: I. Koulouridis, T. Hocine, B.L. Jaber
Drafting of the article: I. Koulouridis, B.L. Jaber
Critical revision of the article for important intellectual content: B.L. Jaber, Nicolaos E. Madias, David M. Kent, Jessica K. Paulus
Final approval of the article: B.L. Jaber, T. Hocine, Nicolaos E. Madias, David M. Kent, Jessica K. Paulus, M. Alfayez, I. Koulouridis
Provision of study materials or patients: B.L. Jaber
Statistical expertise: T. Hocine, B.L. Jaber
Administrative, technical, or logistic support: not applicable
Collection and assembly of data: I. Koulouridis, M. Alfayez

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FIGURES LEGENDS

Figure 1: Flow diagram describing the derivation of the analytical dataset.

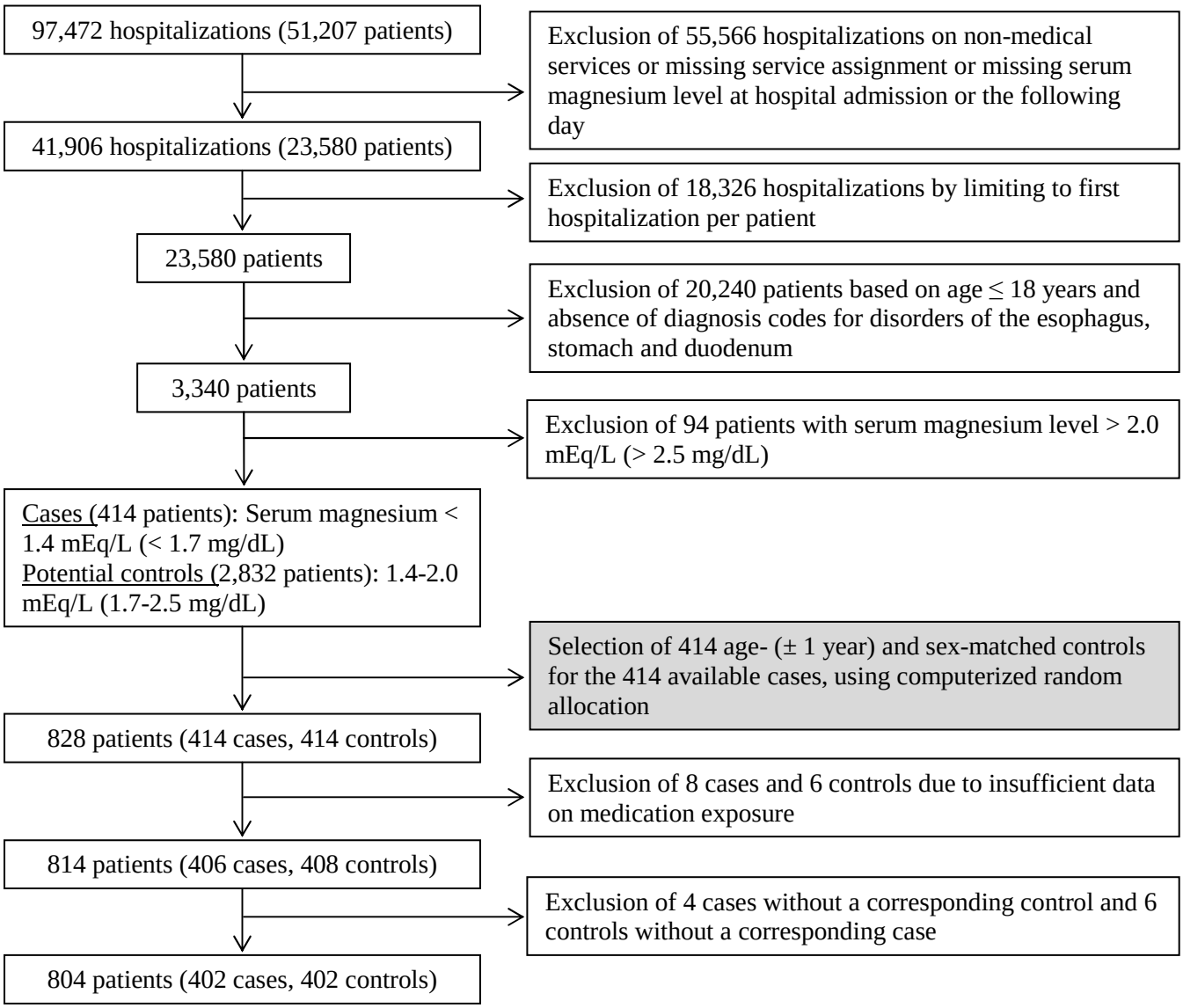


Table 1: Characteristics of cases (serum magnesium < 1.4 mEq/L) and control subjects (serum magnesium level 1.4-2.0 mEq/L).

Variable	No. Pairs	Cases	Control subjects	P value
Serum magnesium, mEq/L *	402	1.23 (1.15, 1.32)	1.64 (1.56, 1.81)	-
Age, years	402	70 (14.4)	70 (14.4)	-
Men, n (%)	402	161 (40.0)	161 (40.0)	-
White ethnicity, n (%)	400	327 (81.8)	336 (84.0)	0.463
Charlson-Deyo comorbidity index, n (%)	402			0.037
0		140 (34.8)	158 (39.3)	
1		121 (30.1)	141 (35.1)	
2		70 (17.4)	51 (12.7)	
≥3		71 (17.7)	52 (12.9)	
Diabetes mellitus, n (%)	402	139 (34.6)	106 (26.4)	0.012
GERD, n (%)	402	293 (72.9)	322 (80.1)	0.025
Esophageal disorders (including GERD), n (%)	402	333 (82.8)	348 (86.6)	0.184
Gastro-duodenal disorders, n (%)	402	100 (24.9)	90 (22.4)	0.462
Serum creatinine, mg/dL	399	1.29 (1.15)	1.19 (1.02)	0.191
eGFR, ml/min/1.73m^2	397	67.6 (28.6)	68.9 (25.9)	0.505
Serum calcium, mg/dL	399	8.42 (0.76)	8.63 (0.70)	<0.001
Serum albumin, gm/dL	140	3.13 (0.65)	3.21 (0.70)	0.132
Proton pump inhibitor use, n (%)	402	219 (54.5)	238 (59.2)	0.207
Proton pump inhibitor type, n (%)	402			0.147
Omeprazole		38 (9.5)	48 (11.9)	
Lansoprazole		93 (23.1)	88 (21.9)	
Pantoprazole		58 (14.4)	51 (12.7)	
Rabeprazole		3 (0.7)	5 (1.2)	
Esomeprazole		27 (6.7)	46 (11.4)	
Omeprazole equivalent daily dose, mg/day *	322	5 (0, 20)	12.5 (0, 20)	0.950
Diuretics				
Loop, n (%)	402	66 (16.4)	75 (18.7)	0.452
Potassium sparing, n (%)	402	21 (5.2)	17 (4.2)	0.627
Thiazide, n (%)	402	56 (13.9)	35 (8.7)	0.024

* Median with 25th and 75th percentiles; GERD denotes gastro-esophageal reflux disease; eGFR, estimated glomerular filtration rate;

P values are calculated using paired t-test, McNemar's test or Wilcoxon signed-rank test, where appropriate. Multilevel factorial variables are presented with global P values and were analyzed using conditional logistic regression.

Table 2. Unadjusted and adjusted analyses examining the association of proton pump inhibitor use with hypomagnesemia.

Predictor variable (conditional logistic regression)	Unadjusted analysis			Adjusted analysis		
	No. Pairs	OR (95% CI)	P value	No. Pairs	OR (95% CI)	P value
PPI use						
All matched cases	402	0.83 (0.63, 1.09)	0.207	397	0.82 (0.61, 1.11)	0.193
Matched cases with GERD	215	1.20 (0.81, 1.78)	0.366	210	1.16 (0.76, 1.76)	0.487
Matched cases with esophageal disorders (including GERD)	285	1.00 (0.71, 1.41)	>0.99	282	1.00 (0.69, 1.45)	0.995
Matched cases with serum magnesium $\leq$ 1.0 mEq/L	31	0.55 (0.20, 1.48)	0.232	26	0.78 (0.13, 4.61)	0.786
Matched cases with eGFR >60 ml/min per 1.73m^2	178	0.77 (0.51, 1.16)	0.212	178	0.84 (0.53, 1.34)	0.461
Matched cases with admission medication list	127	0.78 (0.47, 1.27)	0.319	125	0.77 (0.44, 1.36)	0.367
PPI type	402		0.147	397		0.129
None		1.00			1.00	
Omeprazole		0.75 (0.47, 1.18)			0.76 (0.47, 1.24)	
Lansoprazole		0.95 (0.66, 1.36)			0.96 (0.66, 1.42)	
Pantoprazole		1.02 (0.66, 1.58)			0.97 (0.61, 1.53)	
Rabeprazole		0.54 (0.13, 2.31)			0.58 (0.13, 2.65)	
Esomeprazole		0.52 (0.30, 0.89)			0.47 (0.26, 0.83)	
Omeprazole equivalent daily dose (per 10 mg/day increase)	322	0.99 (0.89, 1.10)	0.950	317	0.98 (0.88, 1.10)	0.781

Analyses adjusted for Charlson-Deyo comorbidity index (0, 1, 2, ≥3), diabetes mellitus (yes/no); GERD (yes/no); use of diuretics (yes/no for each diuretic type), and eGFR (ml/min/1.73m^2).

* GERD denotes gastro-esophageal reflux disease; eGFR, estimated glomerular filtration rate

Supplemental Table 1: Review of case reports of PPI-induced hypomagnesemia in current literature.

						Proton pump inhibitor				
Reference	**Year**	**Age (years)**	**Sex**	**Serum magnesium (mEq/L)**	**Urine magnesium (mEq/24h)**	**Type**	**Daily dose (mg)**	**Duration of therapy (years)**	**Diuretic**	**Indication for PPI administration**
Epstein M [8]	2006	51	F	0.8	0	Omeprazole	40	>1	-	Barrett's esophagitis
		80	M	0.4	0.9	Omeprazole	20	"several"	-	-
Metz DC [9]	2007	51	F	-	-	Pantoprazole	160	2	-	Zollinger – Ellison syndrome
Shabajee N [12]	2008	78	F	<0.2	-	Omeprazole	40	7	Yes	Duodenitis
		81	M	0.4	-	Omeprazole	40	-	No	-
Cundy T [10]	2008	67	M	0.2	-	Omeprazole	20	9	No	GERD
		60	F	0.4	-	Omeprazole	40	5	Yes	GERD
François M [11]	2008	62	F	0.6	-	Omeprazole	20	10	-	GERD
Broeren MA [13]	2009	58	M	0.3	0.06	Omeprazole	40	8	No	Esophagitis
Dornebal J [20]	2009	82	M	0.3	-	Esomeprazole	40	9	Yes	Esophagitis
		76	F	0.2	-	Esomeprazole	40	4	No	Peptic ulcer
		61	F	0.2	-	Omeprazole	40	9	Yes	Dyspepsia
Hmu [14]	2009	71	F	0.5	"normal"	Lansoprazole	-	1.5	Yes	Dyspepsia
Kuipers MT [15]	2009	76	F	0.4	0.22	Esomeprazole	40	1	No	GERD
Fernandez [16]	2010	67	M	0.3	-	Omeprazole	20	3	No	NSAID administration
Hoorn EJ [17]	2010	63	M	0.06	1	Esomeprazole	20	11	No	Peptic ulcer
		81	M	0.3	2	Esomeprazole	20	3	No	-
		73	F	0.7	0.4	Pantoprazole	40	1	No	Steroid administration
		62	F	<0.2	<0.2	Omeprazole	20	13	-	Barrett's esophagitis
Regolisti G [21]	2010	65	M	0.4	"high"	Lansoprazole	30	"many"	No	Barrett's esophagitis
Mackay JD [18]	2010	57	F	0.3	-	Omeprazole	-	10	Yes	GERD
		72	F	0.9	-	Omeprazole	-	12	Yes	Peptic ulcer
		75	F	0.4	-	Omeprazole	-	2	Yes	NSAID administration
		74	F	0.6	1.2	Omeprazole	20-40	11	Yes	GERD
		73	F	<0.4	-	Esomeprazole		10	Yes	GERD
		53	F	0.6	-	Omeprazole	-	6	No	GERD
		77	F	0.6	-	Omeprazole	-	10	No	GERD
		69	F	0.6	-	Omeprazole	-	3	Yes	GERD
		76	F	<0.4	-	Omeprazole	-	11	Yes	NSAID administration
		60	M	<0.4	-	Omeprazole	-	10	Yes	GERD
Negri * [19]	2011	59	M	-	"low"	Esomeprazole	-	-	-	-

- Stands for "Not reported"; * Information based on abstract

As shown in the table above, case reports and case series span throughout a 5-year period (2006 – 2011). They comprise 31 patients (20 females, 11 males), with age from 51 to 82 years (mean 68.1 ± 9.3), twenty of which used omeprazole. All of 31 patients used PPIs for more than one year and serum Mg levels were indicative of severe hypomagnesemia, spanning from 0.06 to 0.92 mEq/L (mean 0.43 ± 0.21). The urinary excretion of Mg was low or normal in almost all the cases that presented this information, pointing out to a likely cause of gastrointestinal rather than renal Mg loss however, confirmative studies are lacking [17]. The main symptoms at presentation were related in most cases with the presence of severe electrolyte disorder.

Supplemental Table 2: Inclusion and exclusion criteria and ascertainment of covariates with the corresponding ICD-9-CM codes that were used for the various conditions.

Inclusion criteria
▪ Age ≥ 18 years
▪ First hospitalization
▪ Diseases of esophagus: 530.0, 530.10, 530.11, 530.12, 530.19, 530.20, 530.21, 530.3, 530.4, 530.5, 530.6, 530.7, 530.81, 530.82, 530.83, 530.84, 530.85, 530.86, 530.87, 530.89, 530.9
▪ Gastric ulcer: 531.0, 531.1, 531.2, 531.3, 531.4, 531.5, 531.6, 531.7, 531.9
▪ Duodenal ulcer: 532.0, 532.1, 532.2, 532.3, 532.4, 532.5, 532.6, 532.7, 532.9
▪ Peptic ulcer: 533.0, 533.1, 533.2, 533.3, 533.4, 533.5, 533.6, 533.7, 533.9
▪ Gastrojejunal ulcer: 534.0, 534.1, 534.2, 534.3, 534.4, 534.5, 534.6, 534.7, 534.9
▪ Gastritis & duodenitis: 535.0, 535.1, 535.2, 535.3, 535.4, 535.5, 535.6
▪ Disorders of function of stomach: 536.1, 536.2, 536.3, 536.8
▪ Other disorders of stomach & duodenum: 537.0, 537.1, 537.2, 537.3, 537.5, 537.6, 537.81, 537.82, 537.83, 537.84, 537.89, 537.9
▪ Mucositis: 538
Exclusion criteria
▪ Acute and chronic diarrheal syndromes:
o Diarrhea: 787.91, 006.9, 008.5, 008.41, 008.49, 008.46, 008.8, 008.49, 008.69, 009.2, 009.3, 787.91, 558.2, 556.9, 008.8, 008.62, 008.67
o Enteritis: 558.9, 006.9, 006.0, 006.2, 006.1, 008.46, 004.9, 008.5, 008.49, 008.43, 558.9, 008.45, 008.2, 008.67, 008.2, 008.47, 008.46, 008.42, 008.49, 008.8, 008.69, 008.41, 008.00, 008.04, 008.03, 008.01, 008.02, 008.09, 008.44, 009.00, 009.1, 008.47, 557.0, 487.8, 564.9, 129, 002.9, 003.0, 009.0, 004.9, 008.41, 005.0, 558.2
o Enterocolitis: 557.0, 555.2, 557.1, 557.0, 777.5, 008.45, 558.1, 556.0
o Colitis: 558.9, 006.9, 006.2, 004.9, 558.9, 556.9, 558.1, 009.0, 555.1, 009.0, 009.1, 557.9, 559.0, 557.1, 564.9, 008.45, 557.0, 556.9, 556.0, 557.0, 556.1, 556.5, 556.2, 556.3, 556.8
o Ulcerative colitis: 556.9, 556.0, 557.0, 556.1, 556.5, 556.2, 556.3, 556.8, 556.6
o Crohn's disease: 555.9
o Regional enteritis: 555.9, 555.1, 555.2, 555.0
o Small bowel bypass surgery: 45.91, 45.93, 45.94
▪ Alcoholism: 303.91, 303.92, 303.93, 303.90, 303.01, 303.02, 291.1, 291.2, 291.0, 291.81, 291.3, 303.03, 303.00, 425.5, 571.2
▪ Pancreatitis: 577.0, 577.1, 577.2, 577.8
▪ Primary hyperparathyroidism, primary hyperaldosteronism: 259.3, 252.00, 252.01, 252.02, 252.08, 255.10
▪ Kidney transplantation: 55.69
▪ Cardiopulmonary by-pass: 39.61, 39.66
▪ Admission to all surgical services, obstetrics/gynecology, orthopedics, psychiatry, medical oncological services, absence of service assignment.
Covariates
▪ Drugs prior to the admission: proton pump inhibitors; loop, thiazide and potassium sparing diuretics; aminoglycosides; amphotericin B; chemotherapeutic and immunosuppressive agents; pentamidine
▪ Diabetes: 250.00, 250.01, 250.02, 250.03, 250.1x, 250.2x, 250.3x, 250.4x, 250.5x, 250.6x, 250.7x, 250.8x, 250.9x
▪ Charlson-Deyo comorbidity index
▪ Serum creatinine
▪ Gastro-esophageal reflux disease: 530.81

Supplemental Table 3: Structured data collection form of medication exposure at the time of admission.

Date of Hospitalization: *MRN:* *Account No:*

Proton Pump Inhibitors

Generic name	Brand name	Daily dose (mg/day)	Route	Duration (months)
☐ Omeprazole	Losec, Prilosec, Zegerid	☐10 ☐20 ☐40 ☐60 ☐120 ☐360☐___	p.o.	
☐ Lansoprazole	Prevacid	☐15 ☐30 ☐60 ☐90 ☐180☐___	p.o.	
☐ Pantoprazole	Protonix	☐40 ☐80 ☐160☐240☐___	☐p.o. ☐i.v.	
☐ Rabeprazole	Aciphex	☐20 ☐40 ☐60 ☐120	p.o.	
☐ Esomeprazole	Nexium	☐20 ☐40 ☐80 ☐240 ☐___	☐p.o. ☐i.v.	
☐ Dexlansoprazole	Dexilant, Kapidex	☐30 ☐60 ☐___	p.o.	

Loop Diuretics

Generic name	Brand name	Daily dose (mg/day)	Route	Duration (months)
Bumetanide	Bumex			
Etacrynic Acid	Edecrin			
Furosemide	Lasix, Furosemide			
Torsemide	Demadex			

Potassium Sparing Diuretics

Generic name	*Brand name*	*Daily dose (mg/day)*	*Route*	*Duration (months)*
Amiloride	Amiloride Hydrochloride, Midamor, Moduretic			
Eplerenone	Inspra			
Spironolactone	Aldactone, Aldactazide			
Triamterene	Dyrenium			

Thiazides

Generic name	Brand name	Daily dose (mg/day)	Route	Duration (months)
Hydrochlorothiazide	Dyazide, Microzide			
Chlorothiazide	Diuril			
Chlorthalidone	Thalitone			
Hydroflumethiazide	Diucardin, Salutensin			
Indapamide	Lozol			
Methyclothiazide	Methyclothiazide, Aquatensen, Enduron			
Polythiazide	Renese			
Trichlormethiazide	Diurese, Metahydrin, Naqua, Aquacot			

Aminoglycosides

Generic name	Brand name	Daily dose (mg/day)	Route	Duration (months)
Amikacin	Amikin			
Gentamicin	Gentamicin, Genoptic, Gentak, Garamycin, Cidomycin, Septopal, Pred-G			
Tobramycin	Tobradex, Tobrex, Tobramycin(inj), Tobi			

Anti-fungal

Generic name	*Brand name*	*Daily dose (mg/day)*	*Route*	*Duration (months)*
Amphotericin B	Abelcet(inj), Ambisome(inj), Fungizone			

Cancer Chemotherapeutic Agents and Immunosuppressive Agents

Generic name	Brand name	Daily dose (mg/day)	Route	Duration (months)
Cisplatin	Cisplatin(inj), Platinol(inj)			
Cyclosporine	Neoral, Restasis, Sandimmune, Gengraf			
Tacrolimus	Prograf, Protopic			
Cetuximab	Erbitux(inj)			
Panitumumab	Vectibix(inj)			

Anti-protozoal

Generic name	Brand name	Daily dose (mg/day)	Route	Duration (months)
Pentamidine	NebuPent			

Supplemental Table 4: Study sample characteristics and univariate analyses between cases and controls. Only pairs with no missing values were used in the analyses.

	Continuous Variables					
	Cases	Controls	No. Pairs	Statistic	P value	OR (95% CI) derived from conditional logistic regression
Magnesium, mEq/L *	1.23 (1.15, 1.32)	1.64 (1.56, 1.81)	402	-	-	-
Age, years	70 (14.4)	70 (14.4)	402	-	-	-
Creatinine, mg/dL	1.29 (1.15)	1.19 (1.02)	399	Paired t-test	0.191	1.09 (0.96, 1.25)
eGFR, ml/min/1.73m^2	67.6 (28.6)	68.9 (25.9)	397	Paired t-test	0.505	1.00 (0.99, 1.00)
PPI dose * †	5 (0, 20)	12.5 (0, 20)	322	Wilcoxon signed rank test	0.950	0.99 (0.89, 1.10)
Calcium, mg/dL	8.42 (0.76)	8.63 (0.70)	399	Paired t-test	<0.001	0.68 (0.56, 0.83)
Albumin, mg/dL	3.13 (0.65)	3.21 (0.70)	140	Paired t-test	0.132	0.78 (0.56, 1.08)
Length of stay, days *	5 (3, 9)	4 (2, 7)	402	Wilcoxon signed rank test	0.004	1.03 (1.00, 1.06)
Total hospitalizations *	2 (1, 4)	2 (1, 3)	402	Wilcoxon signed rank test	0.124	1.01 (0.98, 1.05)
	Categorical Variables					
	Cases (%)	Controls (%)	No. Pairs	Statistic	P value	OR (95% CI) derived from conditional logistic regression
PPI use (hardcopies)	21 (52.5)	25 (62.5)	40	McNemar's test	0.480	0.64 (0.25, 1.64)
PPI use (electronic)	219 (54.5)	238 (59.2)	402	McNemar's test	0.207	0.83 (0.63, 1.09)
PPI type (electronic)					0.147 (global)	Not applicable
None	183 (45.5)	164 (40.8)			Reference	Reference
Omeprazole	38 (9.5)	48 (11.9)			0.211	0.75 (0.47, 1.18)
Lansoprazole	93 (23.1)	88 (21.9)	402	Conditional Logistic Regression	0.764	0.95 (0.66, 1.36)
Pantoprazole	58 (14.4)	51 (12.7)			0.935	1.02 (0.66, 1.58)
Rabeprazole	3 (0.7)	5 (1.2)			0.406	0.54 (0.13, 2.31)
Esomeprazole	27 (6.7)	46 (11.4)			0.017	0.52 (0.30, 0.89)
Men	161 (40.0)	161 (40.0)	402	-	-	-
White ethnicity	327 (81.8)	336 (84.0)	400	McNemar's test	0.463	0.86 (0.60, 1.23)
Charlson-Deyo index					0.037 (global)	Not applicable
0	140 (34.8)	158 (39.3)			Reference	Reference
1	121 (30.1)	141 (35.1)	402	Conditional Logistic Regression	0.872	0.97 (0.70, 1.35)
2	70 (17.4)	51 (12.7)			0.039	1.58 (1.02, 2.43)
≥3	71 (17.7)	52 (12.9)			0.050	1.52 (1.00, 2.31)
Diabetes	139 (34.6)	106 (26.4)	402	McNemar's test	0.012	1.51 (1.10, 2.06)
Loop diuretics	66 (16.4)	75 (18.7)	402	McNemar's test	0.452	0.85 (0.59, 1.23)

Potassium sparing diuretics	21 (5.2)	17 (4.2)	402	McNemar's test	0.627	1.24 (0.65, 2.34)
Thiazide diuretics	56 (13.9)	35 (8.7)	402	McNemar's test	0.024	1.72 (1.09, 2.72)
Aminoglycosides	1 (0.2)	0 (0.0)	402	-	-	-
Anti-fungal	0 (0.0)	0 (0.0)	402	-	-	-
Chemotherapeutic & Immunosuppressive	3 (0.7)	0 (0.0)	402	-	-	-
Anti-protozoal	0 (0.0)	0 (0.0)	402	-	-	-
GERD	293 (72.9)	322 (80.1)	402	McNemar's test	0.025	0.67 (0.50, 0.92)
Diseases of esophagus (including GERD)	333 (82.8)	348 (86.6)	402	McNemar's test	0.184	0.76 (0.52, 1.11)
Diseases of stomach & duodenum	100 (24.9)	90 (22.4)	402	McNemar's test	0.462	1.14 (0.83, 1.58)

- stands for Not Performed; * correspond to variables with non-normal distribution expressed in median with 25^{th} and 75^{th} percentiles whereas the remaining variables are normally distributed and expressed in mean with SD; † Omeprazole equivalent daily dose in mg/24 (OR is expressed per 10mg/24h);
The global statistical significance of multi-level factorial variables was tested by removing the variable of interest from the conditional logistic regression model and conducting a likelihood ratio (LR) test between these two nested models.

Supplemental Table 5: Multivariate conditional logistic regression analyses examining the association of case status with PPIs and covariates of interest. These models were fitted in the entire dataset and only pairs with no missing values were used in the analyses.

	1st model (397 pairs)		2nd model (397 pairs)		3rd model (317 pairs)	
Predictor	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Proton pump inhibitor use	0.87 (0.61, 1.11)	0.193	-	-	-	-
Proton pump inhibitor type						
None	-		1.00		-	
Omeprazole	-		0.76 (0.47, 1.24)		-	
Lansoprazole	-	-	0.96 (0.66, 1.42)	0.129	-	-
Pantoprazole	-		0.97 (0.61, 1.53)		-	
Rabeprazole	-		0.58 (0.13, 2.65)		-	
Esomeprazole	-		0.47 (0.26, 0.83)		-	
Proton pump inhibitor dose *	-	-	-	-	0.98 (0.88, 1.10)	0.781
Diabetes	1.42 (1.01, 1.99)	0.041	1.48 (1.05, 2.07)	0.025	1.40 (0.97, 2.01)	0.072
eGFR†	1.00 (0.99, 1.01)	0.967	1.00 (0.99, 1.01)	0.983	1.00 (0.99, 1.01)	0.921
Loop diuretics	0.82 (0.55, 1.23)	0.338	0.81 (0.54, 1.22)	0.307	0.74 (0.47. 1.17)	0.195
Potassium Sparing Diuretics	1.01 (0.51, 2.01)	0.971	1.01 (0.50, 2.02)	0.984	1.01 (0.46, 2.21)	0.985
Thiazides	1.95 (1.18, 3.22)	0.009	2.00 (1.20, 3.32)	0.007	1.92 (1.11, 3.33)	0.020
Charlson-Deyo index						
0	1.00		1.00		1.00	
1	1.00 (0.71, 1.42)	0.084	1.03 (0.72, 1.46)	0.100	1.08 (0.73, 1.61)	0.056
2	1.57 (0.98, 2.52)		1.58 (0.98, 2.54)		1.68 (0.97, 2.92)	
≥3	1.55 (0.97, 2.48)		1.56 (0.97, 2.52)		1.85 (1.09, 3.15)	
GERD	0.74 (0.54, 1.04)	0.079	0.74 (0.53, 1.04)	0.082	0.66 (0.45, 0.96)	0.031

- stands for Not performed; * Omeprazole equivalent daily dose (OR is expressed per 10mg/24h); † OR is expressed per 1ml/min/1.73m^2 increase
The global statistical significance of multi-level factorial variables was tested by removing the variable of interest from the conditional logistic regression model and conducting a likelihood ratio (LR) test between these two nested models.

Supplemental Table 6: Diagnostic Performance Characteristics of the 2 Out-Of-Hospital PPI Use Ascertainment Methods

Out-of-hospital use of PPIs was ascertained by reviewing admission notes and discharge summaries documented in the electronic medical record (*method 1*) using a structured data collection form. If the hospital admission medication list was not present in these source documents, the nursing electronic medication administration record (*method 2*) for the corresponding hospitalization was reviewed. In this case, PPI use was considered only if prescribed during the total length of the hospitalization and at time of hospital discharge. Performance characteristics of the 2 methods (index tests) were explored in approximately 30% of the sample, by randomly selecting 239 patients and conducting a manual review of hardcopies of the medical records (gold standard test).

		Hardcopies of medical records	
		PPI users	non users
Method 1	PPI users	72	2
	non users	7	48

		Hardcopies of medical records	
		PPI users	non users
Method 2	PPI users	49	28
	non users	9	24

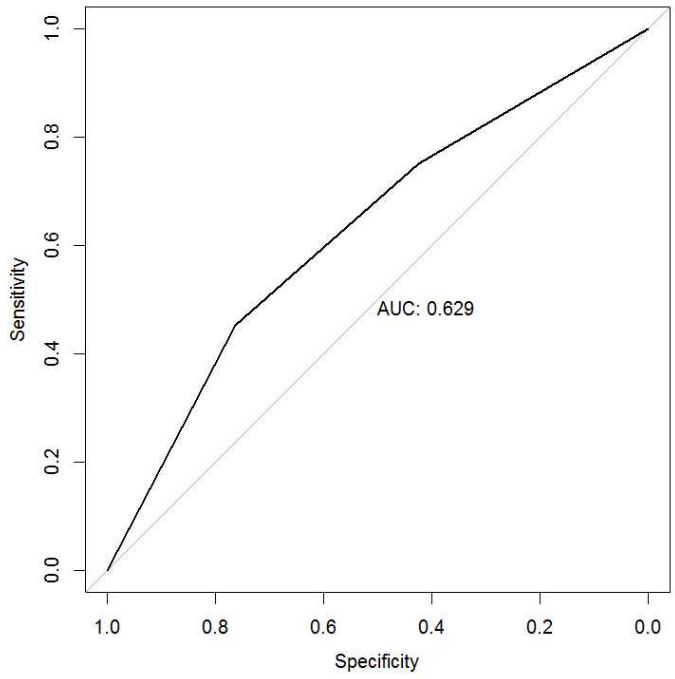
	Method 1	*Method 2*
Sensitivity% (95% CI)	91.1 (82.6, 96.4)	84.5 (72.6, 92.7)
Specificity% (95% CI)	96.0 (86.3, 99.5)	46.2 (32.2, 60.5)
PPV% (95% CI)	97.3 (90.6, 99.7)	63.6 (51.9, 74.3)
NPV% (95% CI)	87.3 (75.5, 94.7)	72.7 (54.5, 86.7)
Accuracy (95% CI)	93.0 (87.2, 96.8)	66.4 (56.7, 75.1)

Supplemental Diagnostics 1: Testing for interactions between PPI use and covariates.

We tested our primary conditional logistic regression model for differential effects of PPI use by adding interaction terms between PPI use and every covariate. None of these interaction terms changed the model in a statistically significant way, according to the likelihood ratio test between the model with all the interaction terms and the primary model ($p = 0.465$).

Supplemental Diagnostics 2: Testing for collinearity between Charlson-Deyo index and diabetes.

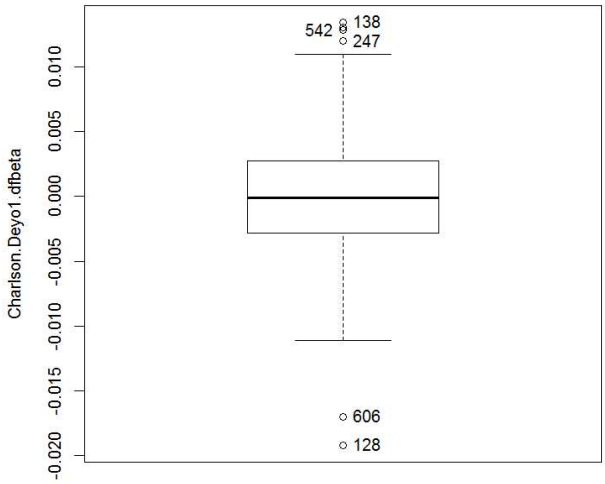
Since Charlson-Deyo comorbidity index captures also diabetes, a potential collinearity between these variables was ruled out by performing simple univariate logistic regression with Charlson-Deyo as a predictor and diabetes as outcome. As depicted below, the area under the curve (AUC) for this model is 0.629 (95% CI 0.588, 0.669).The lowest cut-off point for a mediocre capability of prediction is considered to be 0.75. This means that the model cannot adequately predict diabetes using the Charlson-Deyo index and, therefore, there is not significant collinearity between diabetes and Charlson-Deyo comorbidity index.

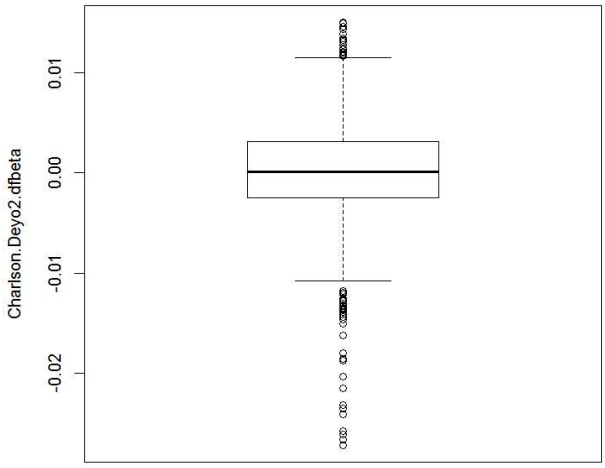


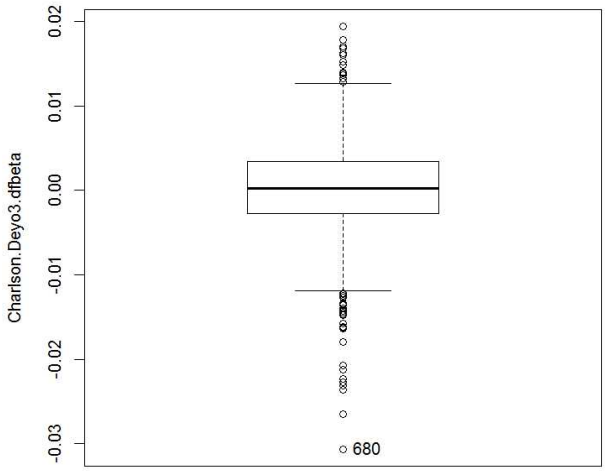
Additionally, the Spearman correlation coefficient between Charlson-Deyo index and diabetes is low (0.215); indicative of absence of significant collinearity between these two predictors.

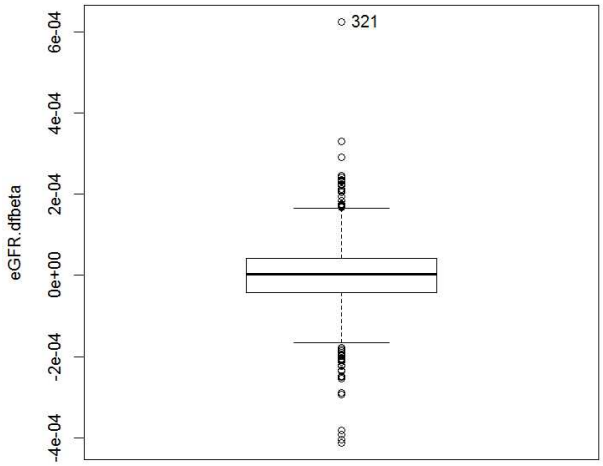
Supplemental Diagnostics 3: Evaluation of primary model by removing influential observations.

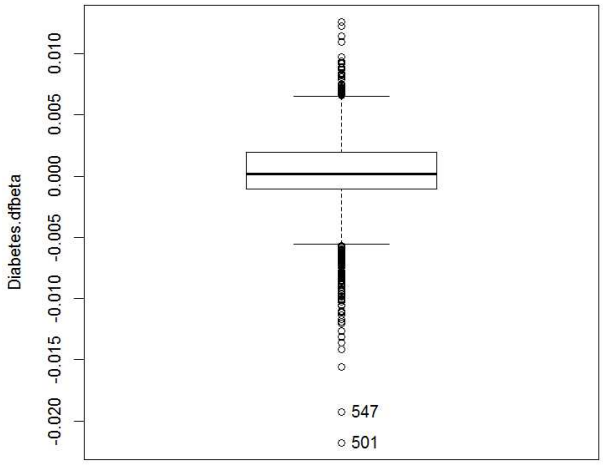
We calculated the DFBETA and standardized DFBETA (DFBETAS) for every predictor in the model and then we identified potential influential points with the use of boxplots.







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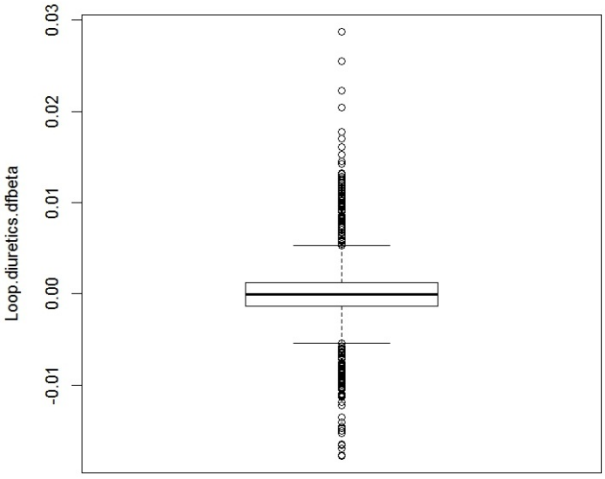
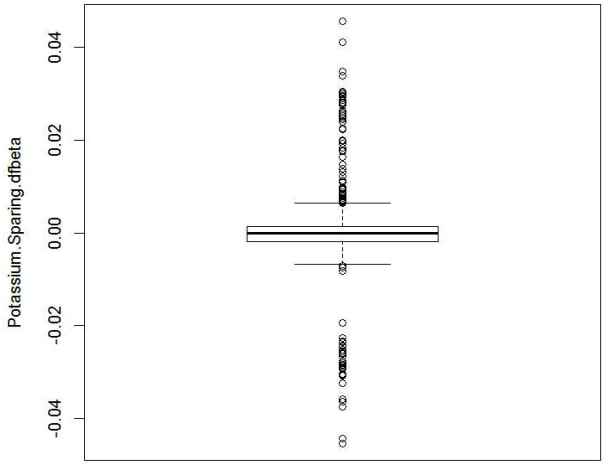
0.005
0.000
-0.005
-0.010
-0.015
-0.020
547
501


Loop.diuretics.dfbeta
0.03
0.02
0.01
0.00
-0.01


Potassium.Sparing.dfbeta
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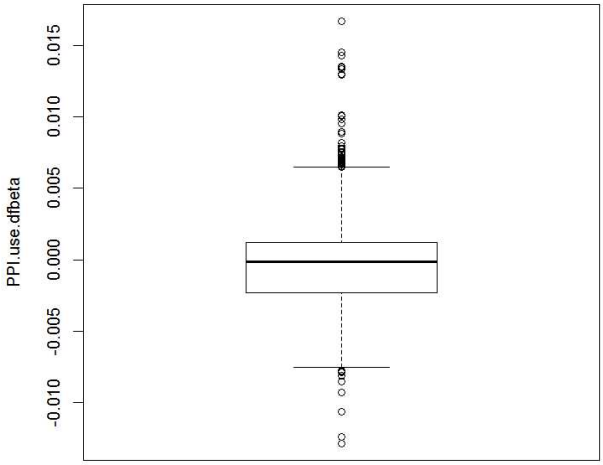
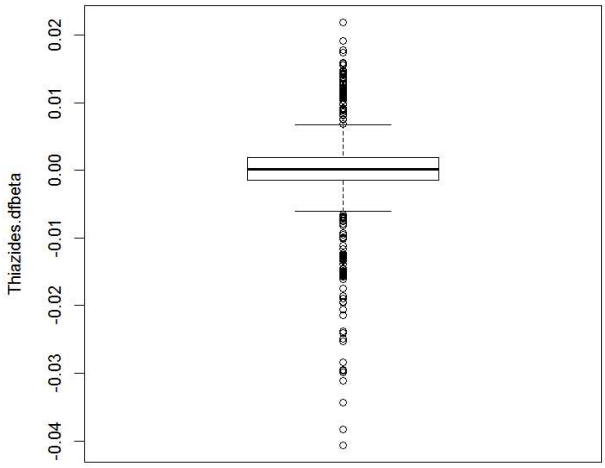
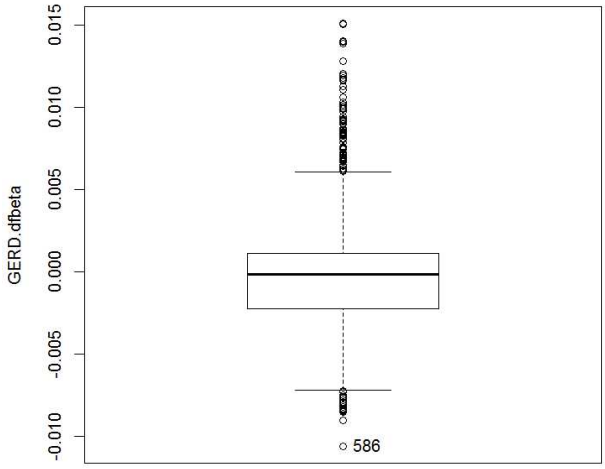
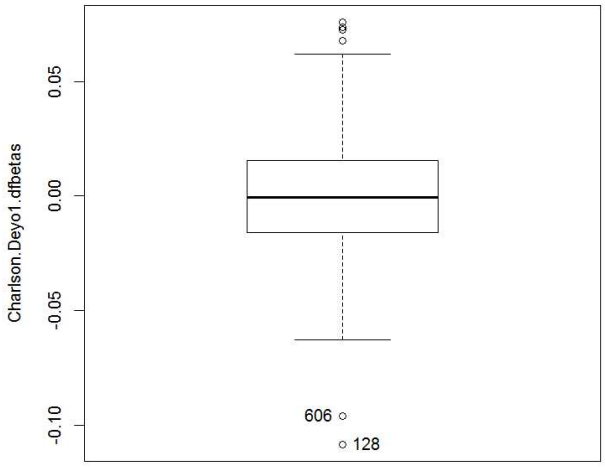
0.02
0.00
-0.02
-0.04

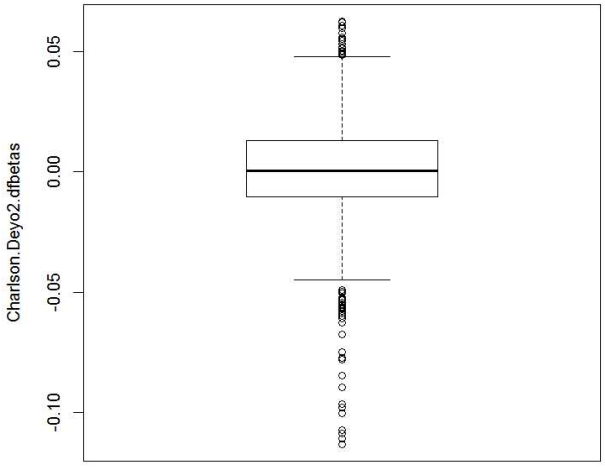

PPI.use.dfbeta
0.015
0.010
0.005
0.000
-0.005
-0.010

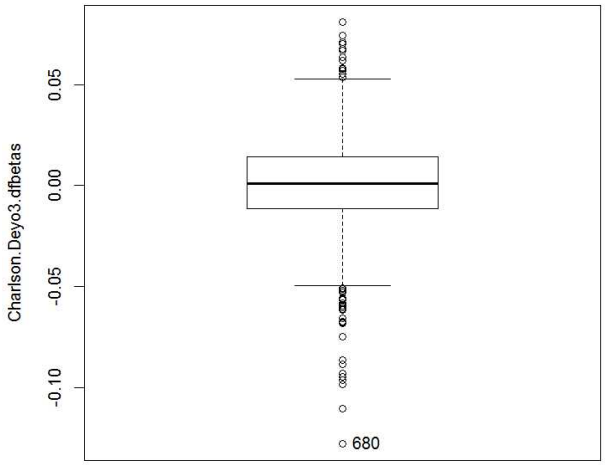


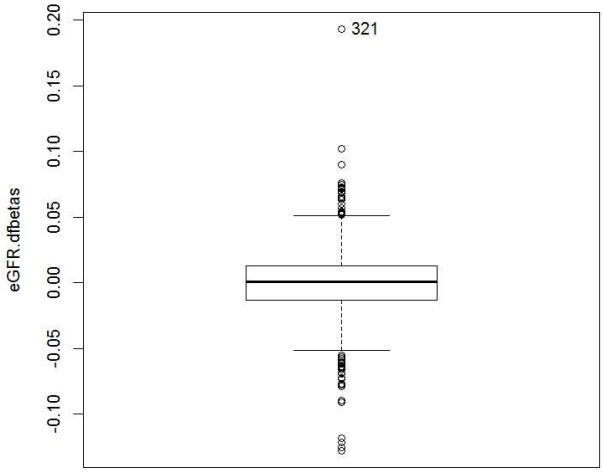


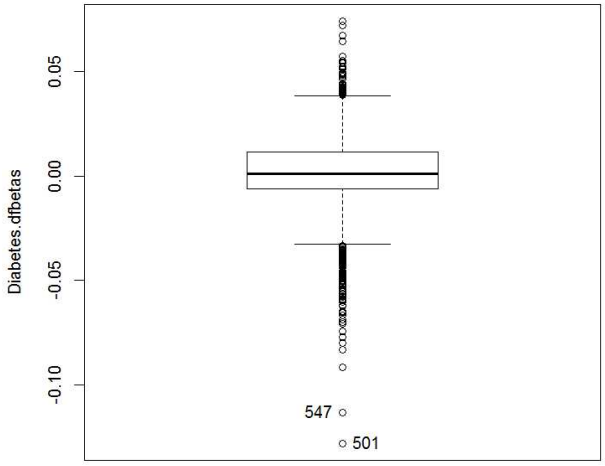
From the above boxplots of DFBETA we identified as potential influential points the following 7 observations: 128, 321, 501, 547, 586, 606, and 680.

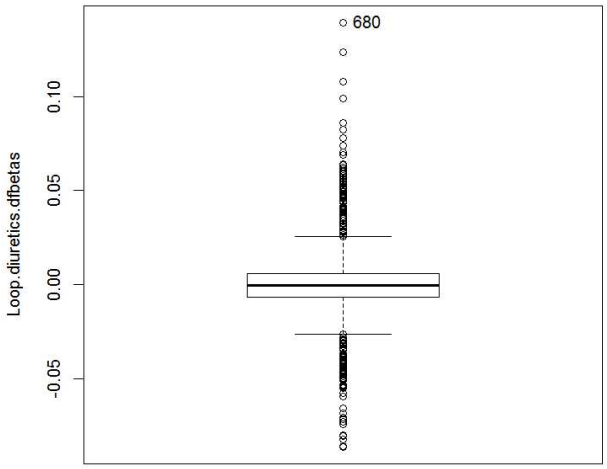


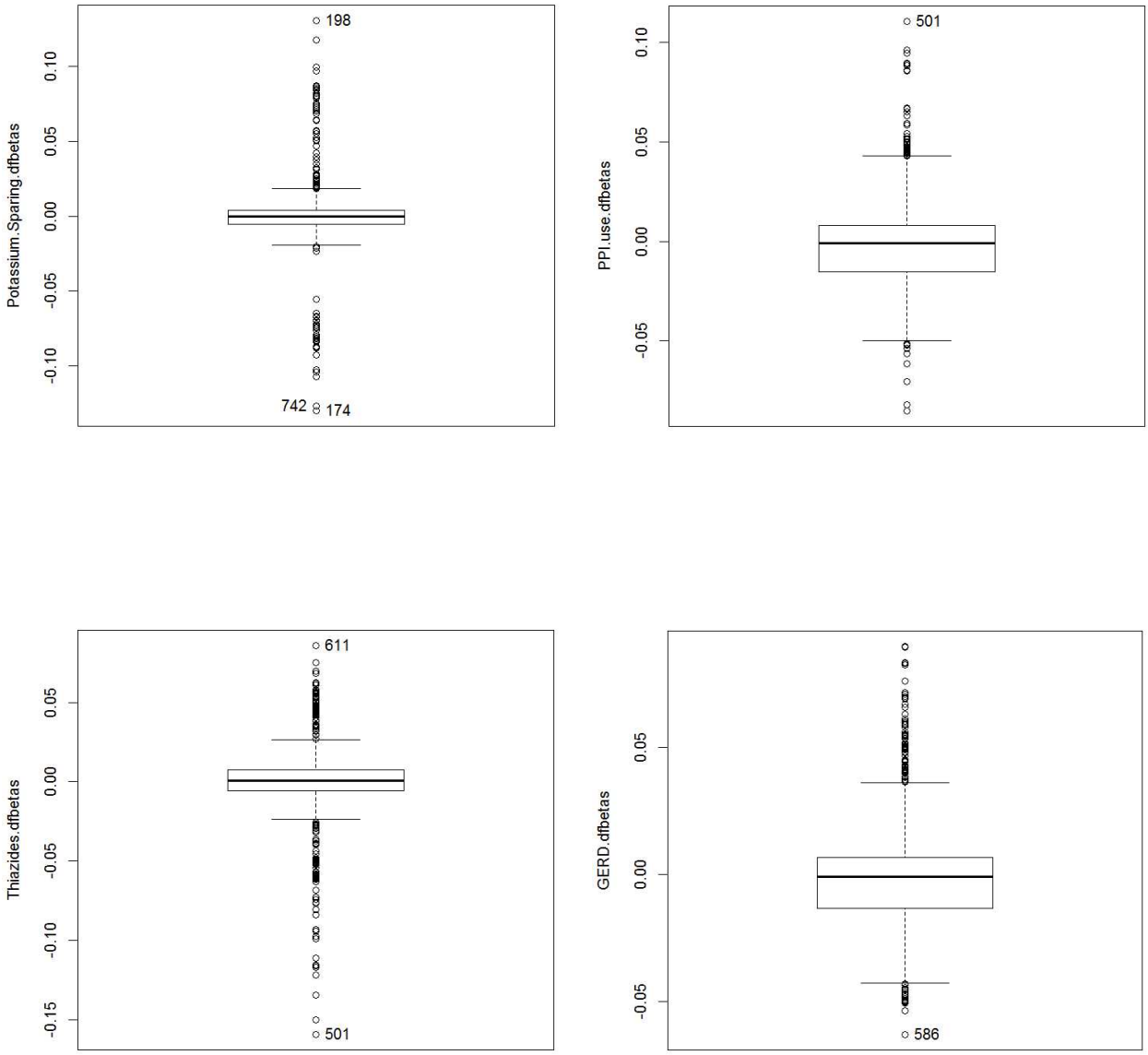



Charlson.Deyo3.dfbetas
0.05
0.00
-0.05
-0.10
680


eGFR.dfbetas
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
321


Diabetes.dfbetas
0.05
0.00
-0.05
-0.10
547
501


Loop.diuretics.dfbetas
0.10
0.05
0.00
-0.05
680



From the above boxplots of standardized DBFETA (DFBETAS) we identified as potential influential points the following 7 observations: 128, 321, 501, 547, 586, 606, and 680 (coincidentally they are the same as the ones identified with DFBETA). All 7 represented cases and 6 among them represented female patients. The OR for PPI use without these observations remains approximately the same (OR 0.76; 95% CI 0.56, 1.03) with the primary model using the full dataset (OR 0.82; 95% CI 0.61, 1.11), implying an overall good fit of our primary model.

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