Proton pump inhibitors use and the risk of chronic kidney disease: a prospective cohort study

Xingyu Zhang[1], Qiangsheng He[2], Zhong Jing[3], Jin-Qiu Yuan[2], and Xiaoyu Dai[1]

[1]Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China
[2]The Seventh Affiliated Hospital Sun Yat-sen University
[3]Sichuan Mianyang 404 Hospital

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Abstract

Background: Proton pump inhibitors (PPIs) are widely used worldwide and have been linked to kidney diseases. However, it remains unclear about the role of PPI use in the development of chronic kidney disease (CKD). Aims: To examine the association between PPI use and risk of CKD. Methods: This is a prospective analysis of 472,373 participants free of any renal failure diagnosis from the UK Biobank. Incident CKD was identified based on medical history and linkage to data on primary care and hospital admissions. Self-reported PPI use was firstly assessed using a touchscreen questionnaire, and then confirmed by a trained staff. We estimated the hazard ratios (HRs) and confidence interval (CIs) with Cox regression models adjusting for potential confounders. The number needed to harm (NNH) was calculated at one and five years of follow-up. Results We documented 7,291 cases of CKD over a median of 8.1 years follow-up. After adjustment for potential confounders, regular PPI users had a 24% increased risk of CKD incident compared to non-regular PPI users (HR1.24, 95%CI1.16 -1.33). The NNH was 773.1 and 177.5 for one and five years of follow-up, respectively. Directly compared with H2 receptor antagonist, a less potent acid suppressor, PPI use was associated with 17% higher risk of CKD (HR 1.17, 95% CI 1.00 to 1.36). Conclusions Regular use of PPI is associated with an increased risk of CKD. Healthcare providers should carefully weigh up the potential benefits against risk in prescribing PPIs, particularly for long-term continuous use.

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Xing-Yu Zhang[1*], Qiang-Sheng He[2*], Zhong Jing[3*], Jin-Qiu Yuan[2#]and Xiao-Yu Dai[1#]

1. Department of Nephrology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China 2. Clinical Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong; Scientific Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China

3. Department of Nephrology, Mianyang 404 Hospital, Mianyang, China

*These authors have contributed equally to this work

#Corresponding Authors:

Jin-Qiu Yuan, Clinical Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong; Scientific Research Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China;

e-mail: yuanjinqiu2006@163.com.

Xiao-Yu Dai, Department of Nephrology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China; e-mail:daixy001@163.com

Summary

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Aims : To examine the association between PPI use and risk of CKD.

Methods: This is a prospective analysis of 472,373 participants free of any renal failure diagnosis from the UK Biobank. Incident CKD was identified based on medical history and linkage to data on primary care and hospital admissions. Self-reported PPI use was firstly assessed using a touchscreen questionnaire, and then confirmed by a trained staff. We estimated the hazard ratios (HRs) and confidence interval (CIs) with Cox regression models adjusting for potential confounders. The number needed to harm (NNH) was calculated at one and five years of follow-up.

Results We documented 7,291 cases of CKD over a median of 8.1 years follow-up. After adjustment for potential confounders, regular PPI users had a 24% increased risk of CKD incident compared to non-regular PPI users (HR1.24, 95%CI1.16 -1.33). The NNH was 773.1 and 177.5 for one and five years of follow-up, respectively. Directly compared with H2 receptor antagonist, a less potent acid suppressor, PPI use was associated with 17% higher risk of CKD (HR 1.17, 95% CI 1.00 to 1.36).

Conclusions Regular use of PPI is associated with an increased risk of CKD. Healthcare providers should carefully weigh up the potential benefits against risk in prescribing PPIs, particularly for long-term continuous use.

Keywords: Proton pump inhibitors, chronic kidney disease, UK Biobank

INTRODUCTION

Proton pump inhibitors (PPIs) are primarily indicated for both the treatment and prevention of acid-related disorders, such as gastroesophageal reflux disease[GERD], peptic ulcers and non-steroidal anti-inflammatory drugs [NSAIDs] bleeding prophylaxis.[1] Given the combination of high efficacy with low toxicity and safety of short-term use, PPIs widely prescribed and are among the top 10 most frequently used classes of drugs worldwide.[2,3] However, the overutilization of PPIs became health concern, and 40% to 60% were taking a PPI with no appropriate indication.[4] Overutilization of PPIs not only increased heathcare cost expenditure but have also been linked to various adverse effects.[4] Observational studies have shown that long-term use of PPIs was associated with *Clostridium difficile* infection, community-acquired pneumonia, hypomagnesemia, bone fractures, rheumatoid arthritis and type 2 diabetes[5-9]. Concerns have been raised about increased risk of kidney disease in PPIs users.

Chronic Kidney Disease (CKD) is a condition where kidneys fail to function optimally. It is characterized by progressive loss of kidney function that can eventually result in end-stage renal disease (ESRD).[10] CKD is an important contributor to morbidity and mortality worldwide with a global prevalence of CKD 9.1% in 2017, resulting in 35.8 million disability-adjusted life years and 1.2 million deaths.[11]Risk factors influencing CKD are complex, including the unhealthy lifestyles, obesity, cardiovascular disease, diabetes mellitus (DM), hypertension and inappropriate drugs use.[11-13] The growing drugs use, like NSAIDs, may also be a contributor to the higher prevalence of CKD.[13,14] There is a growing evidence that PPI use might affect kidney function and thus result in CKD.[15-18] A meta-analysis of three observational studies found that PPI use was associated with increased risk of CKD (risk ratios [RR] 1.29, 95% Confidence Interval [CI], 1.22–1.36).[16] These observational studies are thought-provoking but have important limitations to the evidence base, such as either inadequate assessment of exposures through retrospective recall or administrative claims data, or insufficient adjustment of important confounders such as lifestyle habits.[1,16]A recent randomized controlled

trial including over 17 000 participants found that Pantoprazole seemed to have a modest, although not statistically significant, greater risk of CKD compared with placebo (OR 1.17; 95% CI 0.94 to 1.15).[19] However, this trial was questioned with a short follow-up time and insufficient statistical power.[20,21]

Given the high prevalence of both PPIs use and CKD incident, understanding their association may have important influence on the clinical practice. We therefore performed this prospective cohort study to examine the association between PPI use and incident CKD in the general population using the UK biobank dataset.

Methods

Study and participants

UK Biobank is a well-characterized prospective cohort study of 500,000 individuals aged 40–69 years who were recruited from 21 assessment centers across U.K.. In 2006-2010, eligible participants were invited to visit the closest assessment center to complete the baseline assessment, including a touchscreen questionnaire, physical measures and biological samples collection. Further details about the UK Biobank cohort have been published elsewhere.[22]The UK Biobank study have been approved by the North West Multi-centre Research Ethics Committee, the England and Wales Patient Information Advisory Group, and the Scottish Community Health Index Advisory Group. All participants provided written informed consent prior to data collection. In the present study, we excluded participants who subsequently withdrew from the study (n=1298), those with cancers diagnosis (n=26 820) and renal failure diagnosis (n=2036) prior to baseline, leaving a total of 472,373 participants included in final analysis.

Assessment of PPIs use

At baseline, self-reported PPI use was firstly assessed from participants using a touchscreen questionnaire, and then confirmed during verbal interview with a trained staff. The recorded type of PPIs included omeprazole, lansoprazole pantoprazole, rabeprazole and esomeprazole. In this study, regular use of PPIs was defined as taking PPIs in most days of week for the last 4 weeks.

Assessment of Outcome

Incident CKD was identified based on medical history and linkage to data on primary care and hospital admissions. We used the chronic renal failure (synonym of CKD) variables provided by UK Biobank, which integrated information from these different data sources (including primary care, hospital admissions, self-report and death register). Details of the algorithms used to identify CKD could be found on the UK Biobank website (*www.ukbiobank.ac.uk*). Participants with prevalent of any type of renal failure were excluded at baseline. At the time of analysis, complete follow-up was available up to 31 October 2017 for England and Wales and 31 October 2016 for Scotland.

Covariates

Covariate information were obtained from touchscreen questionnaire and verbal interview at baseline. Sociodemographic factors (age, sex, ethnicity), lifestyle habits (smoking status, alcohol consumption, sleep time, and dietary intake), multivitamin and mineral supplements intake, and general health (overall health rating and longstanding illness) were self-reported. Index of multiple deprivation based on postcode of residence was determined as a composite measure of socioeconomic status. Blood pressure was measured by research staff. Current concomitant comorbidities (hyperlipidemia, diabetes, cardiovascular disease, esophagitis/Barrettsesophagus, GERD, peptic ulcer, upper gastrointestinal bleeding) were assessed using the same way to assess CKD. Other medication use, including aspirin, non-NSAIDs, acetaminophen, angiotensin-converting enzyme inhibitors[ACEIs], angiotensin II receptor blockers [ARBs], beta-blockers, calcium channel blockers, thiazide diuretics, statin, metformin, histamine-2 receptor antagonists [H2RAs], and anticoagulants/ antiplatelets drugs, were assessed using the same way to assess PPI use. Height and weight were measured by trained research staff and used to calculate body mass index (BMI).

Data Analysis

We calculated person-years from the recruitment date to the date of first diagnosis of CKD, death, or the last date of follow-up, whichever happened first. We fitted Cox regression models with age as the timescale to estimate hazard ratios (HR) and 95% confidence intervals (CI) of PPI use on CKD incidence. First, we stratified the analyses by sex and age at baseline (in years, 37-55, 55-65, [?]65 years). We then fitted multivariable-adjusted models with additional adjustment for ethnicity, socioeconomic status, smoking status, alcohol consumption, physical activity, fruit and vegetable intake, red and process meat intake, BMI, sleep time, multivitamin use, mineral supplements intake, current medical status *(systolic blood pressure,hyperlipidemia, diabetes, CVD, overall health rating, longstanding illness*), and concomitant medication use (including *aspirin, non-aspirin NSAIDs, acetaminophen, ACEIs, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics, statin, metformin*)(model1). To address the possible confounding effect of clinical indications for PPI use, we additionally adjusted for esophagitis/Barretts esophagus, GERD, peptic ulcer, and upper gastrointestinal bleeding, H2RA use and anticoagulants/antiplatelets drugs use. Proportional hazards assumption was checked using Schoenfeld's tests and no violation was shown. For covariates with selections of '*do not know* ' and '*prefer not to answer* ', or with missing data, we included an "unknown/missing" value indicator. Given that PPIs and H2RAs have similar clinical indications, we investigated the association between regular H2RA use and CKD risk and performed a head-to-head comparison between PPIs andH2RAs.To present possible association in a clinically translatable way, we calculated the number needed to harm (NNH) based on the method described by Altman D.G and Andersen P.K.[23]

To evaluate potential effect modifiers, we conducted additional stratified analyses according to sex, age, BMI, smoking status, alcohol consumption, hypertension, diabetes, GERD and clinical indication for PPI use. We performed a number of sensitivity analyses to check the robustness of the primary results. First, we excluded CKD incidents and death cases during the first two years of follow-up to minimize reverse causality. Second, we excluded participants with cardiovascular disease to minimize potential influence of the medical condition. Third, we restricted the analyses to participants with no missing data on any covariates. Lastly, we also performed propensity score matching and inverse treatment probability weights analyses to control for the influence of confounding variables. All analyses were conducted using the R software (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

This study included 472,373 participants in the final analyses. Table 1 showed the baseline characteristics of participants by regular PPI use. At baseline, 46 530 (9.85%) participants reported regular use of PPIs. PPI users tended to be deprived, consumed less alcohol, less physically active, with a higher rate of comorbidities (hyperlipidemia, diabetes, and CVD), and were more likely to use other medications (like aspirin, NSAID sandstatin). As expected, PPI users had higher rate of esophagitis/Barretts esophagus, GERD, peptic ulcer, and upper gastrointestinal bleeding. Regular PPI users also had a poorer self-reported overall health rating, and higher rate of longstanding illness.

During a median follow-up of 8.1 years, we documented 1661 incident CKD events among the 46,530 PPI users (4.53 per 1000 person-years), and 5630 events among 425,843 nonusers (1.65 per 1000 person-years). In the initial age and sex-stratified model, regular PPI users had 2.15 times higher risk of incident CKD as compared to non-users (HR 2.15, 95CI 2.03-2.27) (Table 2).The association was attenuated somewhat, but remained significant after adjustment for potential confounders, including sociodemographic factors, lifestyle habits, presence of comorbidities, and use of other medications (HR1.24, 95%CI 1.17 -1.31).The estimated risk was unchanged after further adjustment for clinical indications for PPI use (HR1.24, 95%CI 1.16-1.33).For easy interpretation, NNHs were calculated based on based on the fully adjusted HR and the CKD incidence among non-PPI users. Every 773.1 (95% CI, 690.3 to 946.5), 406.7 (95% CI, 357.8 to 506.5), and 177.5 (95% CI, 152.8 to 226.5) regular PPI users may result in one CKD case over one, two and five years, respectively (**Figure 1**). Regarding different types of PPIs, we found the increased risk of CKD was associated with Omeprazole and Lansoprazole (HR 1.24, 95%CI 1.14 – 1.34 and 1.26, 1.14 – 1.38, respectively), but not with other PPIs, mainly due to the relative low number of cases (Table 3).

We also found that a slightly stronger association between PPI use and acute kidney injury (AKI). In the

fully adjusted model, regular PPI users had a 30% higher risk of AKI incident (HR 1.30, 95%CI 1.22 – 1.38) (**Table S1**). Given the similar clinical indications for PPIs and H2RAs, we also evaluated the association between regular use of H2RAs use and CKD risk. In the basic model, regular use of H2RAs was associated with a 69% greater risk of CKD (HR 1.69, 95%CI 1.49 – 1.91). However, this association disappeared after adjustment for potential confounders and clinical indications for H2RAs use (HR 1.03, 95%CI 0.91– 1.16) (**Table S2**). Direct comparison showed that PPI use was associated with 17% higher risk of CKD compared with H2RAs use (HR 1.17, 95% CI 1.00 to 1.36) (**Table S3**).

In subgroup analyses, the estimates for risk of CKD associated with PPI use did not differ by age, BMI, smoking status, alcohol consumption, hypertension, diabetes, GERD and clinical indication for PPI use (**Figure 2**). However, the estimated risk of CKD with PPI use seemed to be higher among women than men (p-interactions =0.003). Our primary results remained unchanged in several sensitivity analyses by excluding CKD incidents and death cases identified during the first 2 years of follow-up, excluding the participants with cardiovascular disease, and limiting our analysis to participants with no missing covariate data (**Table S4**). When we applied inverse treatment probability weights based on the propensity scores, the estimated HR for CKD was 1.40 (95 % CI 1.25–1.57). The results of propensity score–matching analysis were similar.

Discussion

In this prospective population-based cohort study of over 0.47 million participants, we found that regular use of PPI was associated with a 24% increased risk of CKD adjusting for several potential confounding variables. The association was likely to be more marked in men than women. Additional analysis showed that H2RA, a less potent acid-suppressor, was not associated with CKD. Similar findings were demonstrated for the outcome of AKI. The association between PPI use and CKD persists across several sensitivity analyses and did not show clear evidence of variance among the major types of PPIs.

There are increasing evidence from observational studies suggesting that long-term use of PPIs is associated with risk of kidney disease, such as interstitial nephritis, acute kidney injury, and chronic kidney disease (CKD)[15,17,24].Lazarus and colleagues using data of 10 482 participants in the Atherosclerosis Risk in Communities study found that PPI users had a 50% higher risk of CKD (HR, 1.50, 95%CI 1.14 -1.96) and validated this findings in a second large cohort of248 751 patients[25]. In addition, Arora et al[18] and Xie et al[15] also found that the risk of kidney disease was 10 -28% higher in patients who used PPIs than in non-usersor H2RAs use. Some systematic review and meta-analysis summarized aforementioned three studies and concluded that PPI use was significantly associated with increased the risks of CKD[17,24,26]. However, lack of adjustment for several important confounders, such as diet, alcohol intake and physical activity, might introduce bias of the findings[27]. Furthermore, PPIs users might have poor health status, which may were considered as key confounder factors,[28,29] but not been controlled in most previous observational studies. In our study, we controlled for these confounders and confirmed that PPI use could increase the risk of CKD.

In addition to aforementioned observational studies, a large randomized controlled trial was conducted to evaluate the safety of PPI pantoprazole among 17 598 participants with a median follow-up of 3 years. The researchers found that pantoprazole was likely to have a modest, although not statistically significant, higher risk of CKD compared with placebo (OR 1.17; 95% CI 0.94 to 1.15).[19] However, the trail had also some limitations, such as insufficient power, a short follow-up time frame, potential selection bias and possible conflicts ofinterests[20,21]. The estimated effect of this trial was smaller than our estimates (HR 1.24). Possible explanations included different population characteristics and follow-up time, the presence of residual confounders, and other biases.

Our results also indicated that women were more likely to a higher risk for CKD associated with PPI use. Similar result was reported that PPI-associated AKI was more frequently among women than men (55.42%vs 44.58%)[30]. Anothercohort study including over 120 000 individuals indicated that the increased of AKI with statin use was more marked in women than men[31]. A similar phenomenon was observed that PPI induced hypomagnesemia occurs more commonly among women than men[32]. Since previous studies

have shown that hypomagnesemia was associated with incidence and mortality of kidney disease[18,33,34], this phenomenon might explain this gender disparity. Another possible explanation for this gender disparity was that drug-induced nephrotoxicity was associated with immune hypersensitivity reaction[35,36], which occurs more commonly in women than men.

The underlying mechanism of the association between PPI use and CKD remain unclear. One possible explanation is that PPIs could increase the risk of acute interstitial nephritis (AIN)[37,38], which may transition to chronic interstitial nephritis, and subsequently result in the development of CKD[39]. Previous study revealed that a significant proportion of patients that suffered PPI-induced AIN did not recover to baseline, having either partial or no renal recovery, possibly because of rapid progression AIN from inflammatory interstitial cellular infiltrates to interstitial fibrosis and chronic interstitial nephritis, especially in those patients with delayed diagnosis or treatment[15,39]. Therefore, CKD might be a long-term complication and consequence of PPI-induced AIN due to incomplete recovery of renal function and chronic interstitial nephritis[39]. In addition, PPI use has been linked to hypomagnesemia, which could cause endothelial dysfunction by promoting atherosclerosis, inducing inflammation and inhibiting endothelial proliferation[33,40], consequently result in the development of CKD[33]. In addition, previous studies found that PPI use was associated with the gut microbiota alterations[41], and diabetes[42], which in turn may increase the risk of CKD[33,43]. More research is required to investigate the underlying mechanisms.

A notable strength of our study is that this study was based on a well-established prospective cohort, which collected detailed information on lifestyle factors, medications use, and health conditions. We were able to fully investigate potential confounding factors that were often not available in administrative medical databases. In addition, the large sample size and event number enabled us to get precisely estimated effects for individual class of PPIs and subgroups. Lastly, a wide of robust sensitivity analyses enhanced the validity of our findings.

This study had several limitations. First, as an observational study, we cannot fully exclude potential confounding effect. PPI users might have poor health status and be more concerned about their personal health, so they may be more likely to receive CKD related tests. However, the residual confounding effect might be small as our analyses were based on model with comprehensive adjustment for clinical indication PPI use, comorbidities and overall health status. Second, because information about PPI use was collected only once in the baseline, we were unable to investigate the effects of time varying covariates and exposures on CKD. Third, we could not investigate the possible dose-response relationship due to insufficient information on dose and duration of PPI use. Lastly, despite the large sample size, this study may not be able to examine the effect of specific types of PPIs such as esomeprazole, rabeprazole and pantoprazole on CKD due to the relative low number of cases.

In conclusion, this large cohort study found that regular use of PPIs was associated with increased risk of CKD. Although the causal relationship cannot be determined with an observational study, given that the large number of PPI users as well as the potential risk of CKD and other adverse effects such as enteric infections, healthcare providers should carefully weigh up the potential benefits against risk in prescribing PPIs, particularly for long-term continuous use. Further researches are needed to confirm our findings and to explore the possible mechanisms.

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AUTHORSHIP

Guarantor of the article: Xiaoyu Dai.

XD and JY conceived of the research. XZ, QH and ZJ analyzed the dataset and wrote the first draft of the manuscript. XD, QH and JY interpreted the results, revised the draft paper, and read and approved the final manuscript.

SUPPORTING INFORMATION

Additional Supporting Information is available online. STROBE Checklist was in the end of Supporting Information

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Table 1. Baseline Characteristics of the Study Populations by PPI use

	Regular PPI use No	Regular PPI use Yes
Number of participants*	**425843**	**46530**
Mean (SD) Age, years	56.5 (8.11)	59.9 (7.29)
Male	196435 (46.1%)	21058 (45.3%)
N (%) White	402225 (94.5%)	44250 (95.1%)
Mean (SD) Index of multiple deprivation	17.1 (13.9)	20.0 (15.8)
Smoking status		
Current	44839 (10.5%)	5328 (11.5%)
Previous	141956 (33.3%)	19281 (41.4%)
Never	239048 (56.1%)	21921 (47.1%)
Alcohol consumption		
Daily or almost daily	87605 (20.6%)	8213 (17.7%)
One to four times a week	210968 (49.5%)	19949 (42.9%)
One to three times a month	48492 (11.4%)	5471 (11.8%)
Special occasions only or never	78778 (18.5%)	12897 (27.7%)

Physical activity		
Low	62645 (14.7%)	8625 (18.5%)
Moderate	140208 (32.9%)	13913 (29.9%)
High	140908 (33.1%)	12585 (27.0%)
Mean (SD) fruit and vegetable intake	4.62 (3.09)	4.61 (3.21)
Mean (SD) red and process meat intake (times/week)	2.81 (1.13)	2.88 (1.11)
Mean (SD) sleep time (hour)	8.13 (1.12)	8.09 (1.37)
BMI	27.2 (4.69)	29.2 (5.13)
Multivitamin use	62113 (14.6%)	8166 (17.5%)
Intake of mineral supplements	91120 (21.4%)	9561 (20.5%)
Mean (SD) systolic blood pressure (mm hg)	139 (19.7)	142 (19.1)
Hyperlipidemia	212875 (50.0%)	32352 (69.5%)
Diabetes	23088 (5.4%)	5404 (11.6%)
CVD	24027 (5.6%)	8832 (19.0%)
Esophagitis/barretts esophagus	2356 (0.6%)	4092 (8.8%)
Gastroesophageal reflux disease	8938 (2.1%)	18720 (40.2%)
Peptic ulcer	4358 (1.0%)	5774 (12.4%)
Upper gastrointestinal bleeding	2217 (0.5%)	1397 (3.0%)
Overall health rating		
Poor	13688 (3.2%)	6259 (13.5%)
Fair	80121 (18.8%)	16714 (35.9%)
Good	255332 (60.0%)	21292 (45.8%)
Excellent	76702 (18.0%)	2265 (4.9%)
Longstanding illness	117678 (27.6%)	27350 (58.8%)
Aspirin use	55564 (13.0%)	11398 (24.5%)
Non-aspirin NSAIDs use	69163 (16.2%)	8039 (17.3%)
Paracetamol use	89671 (21.1%)	15323 (32.9%)
ACEIs use	37531 (8.8%)	8250 (17.7%)
ARBs use	9872 (2.3%)	2712 (5.8%)
Beta-blockers use	23290 (5.5%)	6452 (13.9%)
Calcium channel blockers use	23416 (5.5%)	5406 (11.6%)
Thiazide diuretics use	23949 (5.6%)	4870 (10.5%)
Metformin use	10747 (2.5%)	2711 (5.8%)
Statin use	60405 (14.2%)	15226 (32.7%)
H2RAs use	7669 (1.8%)	2098 (4.5%)
Anticoagulants/antiplatelets use	6063 (1.4%)	2412 (5.2%)

*Values within parenthesis are expressed as percentage.

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; H2RAs, histamine-2 receptor antagonists;CVD, cardiovascular disease; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2. Associations of regular use of PPI with the risk of chronic kidney disease

	Cases/ Person-years	Hazard Ratio [95% Confidence Interval] Age and gender stratified model	Hazard Ratio [95% Confidence Int Multivariable adjusted model 1+
PPI use			
Non-regular PPI user	5630/3417548	1.00[Reference]	1.00[Reference]
Regular PPI user	1661/366674	2.15[2.03, 2.27]	1.24[1.17, 1.31]

+ Multivariable adjusted model 1: additionally adjusted for ethnicity (white, or other), socioeconomic status

(index of multiple deprivation, fifth),smoking status (never smoker, previous smoker, or current smoker), alcohol consumption (daily or almost daily, one to four times a week, one to three times a month, special occasions only or never), physical activity (low, moderate, or high), fruit and vegetable intake ([?]5 portions or <5 portions), red and process meat intake (<twice/week, 2.0-2.9 twice/week, 3.0-3.9 twice/week, >4.0 twice/week), BMI, sleep time (<8 hours, 8 hours, 8 to 9 hours,>9 hours), multivitamin use (yes or no), mineral supplements intake (yes or no), overall health rating (poor, fair, good, excellent) and longstanding illness (yes, no), hyperlipidemia (yes or no), systolic blood pressure, diabetes (yes or no), CVD (yes or no), and medications use, including aspirin, non-aspirin NSAIDs, acetaminophen, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta-blockers, calcium channel blockers, thiazide diuretics, statin, metformin.

++Multivariable adjusted model 3: additionally adjusted for clinical PPI use indication, including esophagitis/Barretts esophagus, GERD, peptic ulcer, and upper gastrointestinal bleeding, H2RA use and Anticoagulants/antiplatelets use.

Table 3. Associations of type of PPIs with chronic kidney disease

	Cases/ Person-years	HR [95% Cl]
Type of PPIs		
No PPI use	5630/3417548	1.00
Omeprazole	1023/237523	1.24[1.14, 1.34]
Lansoprazole	635/127975	1.26[1.14, 1.38]
Esomeprazole	73/18161	1.08[0.85, 1.39]
Rabeprazole	41/8745	1.16[0.85, 1.59]
Pantoprazole	33/7347	1.15[0.81, 1.63]

Estimated effects were based on the fully adjusted model (see footnote in table 2).

Abbreviation: PPI, proton pump inhibitor; HR, Hazard Ratio; CI, Confidence Interval

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