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No Associations Between Regular Use of Proton Pump Inhibitors and Risk of All-Cause and Cause-Specific Mortality: A Population-Based Cohort of 0.44 Million Participants

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INTRODUCTION: **The association between proton pump inhibitors' (PPIs) use and mortality remains unclear.**

METHODS: **This was a prospective analysis of 440,840 UK residents and 13,154 deaths. We evaluated the associations with multivariate Cox regression.**

RESULTS: **After adjusting for confounders, such as over health status and longstanding diseases, the regular use of PPIs was not associated with an increased risk of all-cause mortality and mortality due to neoplasms, circulatory system diseases, respiratory system diseases, digestive system diseases, external causes, and other causes.**

DISCUSSION: **Regular use of PPIs was not associated with an increased risk of all-cause and cause-specific mortality.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C101, http://links.lww.com/AJG/C102, http://links.lww.com/AJG/C103, http://links.lww.com/AJG/C104, http://links.lww.com/AJG/C105, http://links.lww.com/AJG/C106, http://links.lww.com/AJG/C107, http://links.lww.com/AJG/C108, http://links.lww.com/AJG/C109, http://links.lww.com/AJG/C110, http://links.lww.com/AJG/C111, http://links.lww.com/AJG/C112, http://links.lww.com/AJG/C113

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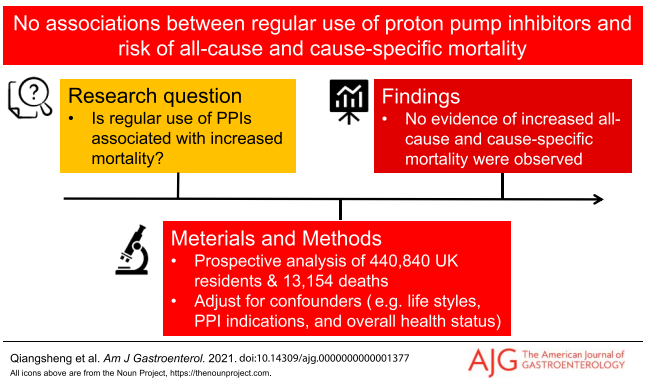

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Table 1. Baseline characteristics of participants by proton pump inhibitor use in the UK Biobank

Characteristics	Regular PPI use		Overall (N = 440,840)
	No (N = 402,775)	Yes (N = 38,065)	
Age, mean (SD), yr	56.2 (8.10)	59.4 (7.43)	56.5 (8.09)
Female, n (%)	221,671 (55.0)	22,120 (58.1)	243,791 (55.3)
White, n (%)	380,449 (94.5)	36,218 (95.1)	416,667 (94.5)
College or university degree, n (%)	137,304 (34.1)	8,519 (22.4)	145,823 (33.1)
Index of multiple deprivation, mean (SD)	16.9 (13.7)	19.3 (15.4)	17.1 (13.9)
Smoking status, n (%)			
Current	41,745 (10.4)	4,121 (10.8)	45,866 (10.4)
Previous	131,464 (32.6)	15,091 (39.6)	146,555 (33.2)
Never	229,566 (57.0)	18,853 (49.5)	248,419 (56.4)
Alcohol consumption, n (%)			
Daily or almost daily	82,958 (20.6)	6,782 (17.8)	89,740 (20.4)
1–4 times a week	200,652 (49.8)	16,594 (43.6)	217,246 (49.3)
1–3 times a month	45,949 (11.4)	4,544 (11.9)	50,493 (11.5)
Special occasions only or never	73,216 (18.2)	10,145 (26.7)	83,361 (18.9)
Physical activity, median (IQR), MET hr/wk	4.00 (3.33)	4.00 (3.33)	4.00 (3.33)
Fruit and vegetable intake (portion), mean (SD)	4.62 (3.09)	4.61 (3.21)	4.61 (3.10)
Sleep time, mean (SD), hr	8.13 (1.10)	8.09 (1.33)	8.13 (1.12)
BMI, mean (SD), kg/m^2	27.1 (4.66)	29.1 (5.11)	27.3 (4.73)
Esophagitis, n (%)	2,097 (0.5)	3,409 (9.0)	5,506 (1.2)
GERD, n (%)	8,098 (2.0)	16,032 (42.1)	24,130 (5.5)
Esophageal stricture, n (%)	268 (0.1)	456 (1.2)	724 (0.2)
Dyspepsia, n (%)	4,383 (1.1)	2,336 (6.1)	6,719 (1.5)
Gastric or duodenal ulcer, n (%)	3,851 (1.0)	4,603 (12.1)	8,454 (1.9)
Upper gastrointestinal tract bleeding, n (%)	1,947 (0.5)	978 (2.6)	2,925 (0.7)
Gastritis, n (%)	7,794 (1.9)	6,171 (16.2)	13,965 (3.2)
Hypertension, n (%)	223,873 (55.6)	26,063 (68.5)	249,936 (56.7)
Hypercholesterolemia, n (%)	193,158 (48.0)	24,580 (64.6)	217,738 (49.4)
Diabetes, n (%)	19,325 (4.8)	3,530 (9.3)	22,855 (5.2)
Mental health disorders, n (%)	27,365 (6.8)	4,839 (12.7)	32,204 (7.3)
COPD, n (%)	938 (0.2)	280 (0.7)	1,218 (0.3)
Asthma, n (%)	44,008 (10.9)	6,523 (17.1)	50,531 (11.5)
Inflammatory bowel disease, n (%)	3,804 (0.9)	707 (1.9)	4,511 (1.0)
Cholelithiasis, n (%)	9,393 (2.3)	2,632 (6.9)	12,025 (2.7)
Rheumatoid arthritis, n (%)	3,719 (0.9)	1,427 (3.7)	5,146 (1.2)
Renal failure, n (%)	931 (0.2)	342 (0.9)	1,273 (0.3)
Anemia, n (%)	3,896 (1.0)	688 (1.8)	4,584 (1.0)
Multivitamin use, n (%)	58,862 (14.6)	6,718 (17.6)	65,580 (14.9)
Intake of mineral supplements, n (%)	87,330 (21.7)	8,215 (21.6)	95,545 (21.7)
Aspirin use, n (%)	39,398 (9.8)	5,307 (13.9)	44,705 (10.1)
Nonaspirin NSAIDs use, n (%)	66,950 (16.6)	6,986 (18.4)	73,936 (16.8)
Paracetamol use, n (%)	84,841 (21.1)	12,522 (32.9)	97,363 (22.1)
ACEIs use, n (%)	29,016 (7.2)	4,806 (12.6)	33,822 (7.7)

Table 1. (*continued*)

Characteristics	Regular PPI use		Overall (N = 440,840)
	No (N = 402,775)	Yes (N = 38,065)	
ARBs use, n (%)	8,255 (2.0)	1,876 (4.9)	10,131 (2.3)
Beta-blockers use, n (%)	14,592 (3.6)	2,831 (7.4)	17,423 (4.0)
Calcium channel blockers use, n (%)	19,149 (4.8)	3,454 (9.1)	22,603 (5.1)
Thiazide diuretics use, n (%)	21,222 (5.3)	3,786 (9.9)	25,008 (5.7)
Metformin use, n (%)	8,798 (2.2)	1,705 (4.5)	10,503 (2.4)
Statin use, n (%)	44,536 (11.1)	8,753 (23.0)	53,289 (12.1)
H2RAs use, n (%)	6,728 (1.7)	1,641 (4.3)	8,369 (1.9)
Anticoagulants/antiplatelets use, n (%)	2,804 (0.7)	641 (1.7)	3,445 (0.8)
Insulin treatment, n (%)	3,300 (0.8)	638 (1.7)	3,938 (0.9)
Overall health rating, n (%)			
Poor	10,813 (2.7)	4,074 (10.7)	14,887 (3.4)
Fair	71,519 (17.8)	12,990 (34.1)	84,509 (19.2)
Good	244,869 (60.8)	18,887 (49.6)	263,756 (59.8)
Excellent	75,574 (18.8)	2,114 (5.6)	77,688 (17.6)
Longstanding illness, n (%)	102,798 (25.5)	20,620 (54.2)	123,418 (28.0)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the top 10 most commonly used medications worldwide. The short-term use of PPIs is generally safe, whereas the long-term use has been linked to various adverse effects, such as bone fractures and chronic kidney disease (1,2). Because the PPI-associated adverse outcomes are serious and each is independently associated with a higher risk of mortality, PPI use may have an effect on death. Many observational studies have evaluated the associations between PPI use and mortality, but the results were conflicting (3–7). For example, a cohort study of 0.21 million participants suggested that PPIs were associated with excessive risk of all-cause mortality, (4) whereas no risk was observed in a recent analysis of 1.9 million US seniors (6). These analyses of administrative data have been limited by a lack of detailed information on lifestyle risk factors and general health status. Confounding effects of these factors cannot be excluded.

For acid-related conditions such as gastroesophageal reflux disease, adherence to PPI treatment is crucial to achieving therapeutic success (8). However, concern about potential adverse outcomes, particularly mortality, is strongly associated with attempts or recommendations for discontinuation in patients and internists (9,10). On the other hand, overprescribing of PPI has also garnered widespread attention (11). Thus, further evaluation of the effects of PPIs on mortality is still required. The aim of this study was to evaluate the independent associations between regular use of PPIs and risk of all-cause and cause-specific mortality based on the UK Biobank.

METHODS

The detailed study method was reported in Supplementary eMethods (see Supplementary Digital Content 1, http://links.lww.com/AJG/C101). Briefly, this study included participants with self-reported personal use of PPIs from the UK Biobank (12). We excluded participants with a diagnosis of cancer or major cardiovascular diseases at baseline and those who subsequently withdrew during the follow-up (see Supplementary Figure S1, Supplementary Digital Content 2, http://links.lww.com/AJG/C102). Regular use of PPIs was initially assessed from participants using a touchscreen questionnaire and then confirmed during verbal interview with a trained staff. "Regular" was defined as most days of the week for the past 4 weeks. The date and cause of death were obtained from death certificates held within the National Health Service (13).

We set a 2-year interval between the time of exposure and incident death, which provided a time window for death occurrence to minimize reverse causality. We calculated person-years from 2 years after the recruitment date to the date of death or the last date of follow-up, whichever happened first. In the basic Cox regression model, we stratified the analyses by sex, age, and indication for PPI use. We adjusted for potential confounders in a series of models (see footnote for Table 2). All analyses were performed using R software (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

This study included 440,840 participants (Table 1). We identified 13,154 cases of deaths over a median follow-up of 5.9 years (range: 4.5–8.8 years). In the basic model, regular use of PPIs was significantly associated with a higher risk of overall mortality (hazard ratio [HR] 1.37, 95% confidence interval 1.29–1.46) (Table 2). However, the effect almost attenuated to null after adjustment for confounders (HR 1.05, 95% confidence interval 0.97–1.13). Our analyses for cause-specific mortality showed similar findings. We observed no associations between regular PPI use with deaths due to neoplasms, circulatory system diseases, respiratory system diseases, digestive system diseases, external causes, and other causes. Additional analyses taking H2RAs as active control also show no

Table 2. Associations of regular use of PPIs with the risk of all-cause and specific-cause mortality

Cause of death	Cases	Person-years	Incidence rate[a]	Hazard ratio (95% confidence interval)			
				Age, sex, and indication-stratified model	Multivariable-adjusted model 1[b]	Multivariable-adjusted model 2[c]	Multivariable-adjusted model 3[d]
All							
Nonregular PPI user	10,177	2,379,305	427.7	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular PPI user	1,680	222,403	755.4	1.37 (1.29–1.46)	1.24 (1.16–1.31)	1.15 (1.08–1.23)	1.05 (0.97–1.13)
Neoplasms (C00-D49)							
Nonregular PPI user	5,896	2,379,305	247.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular PPI user	814	222,403	366	1.20 (1.10–1.31)	1.12 (1.03–1.22)	1.10 (1.01–1.20)	1.06 (0.97–1.15)
Circulatory system diseases (I00-I99)							
Nonregular PPI user	1,871	2,379,305	78.6	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular PPI user	329	222,403	147.9	1.34 (1.16–1.55)	1.15 (1.00–1.33)	1.04 (0.90–1.20)	0.96 (0.83–1.10)
Respiratory system diseases (J00-J99)							
Nonregular PPI user	616	2,379,305	25.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular PPI user	171	222,403	76.9	1.93 (1.56–2.38)	1.67 (1.36–2.05)	1.37 (1.11–1.68)	1.10 (0.90–1.35)
Digestive system diseases (K00-K99)							
Nonregular PPI user	373	2,379,305	15.7	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular PPI user	104	222,403	46.8	2.12 (1.55–2.91)	1.68 (1.23–2.29)	1.39 (1.02–1.91)	1.23 (0.90–1.68)
External causes (V00-Y99)							
Nonregular PPI user	367	2,379,305	15.4	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular PPI user	52	222,403	23.4	1.39 (0.98–1.98)	1.33 (0.94–1.89)	1.20 (0.84–1.71)	1.12 (0.79–1.59)
Other causes (A00-B99, D55-H99, L00-R99, and U00-U49)							
Nonregular PPI user	1,054	2,379,305	44.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular PPI user	210	222,403	94.4	1.71 (1.43–2.04)	1.53 (1.28–1.83)	1.38 (1.15–1.65)	1.14 (0.96–1.36)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
[a]Per 100,000 person-years.
[b]Multivariable-adjusted model 1: additionally adjusted for ethnicity (White and other), socioeconomic status (index of multiple deprivation, fifth), education level (college or university degree, other), smoking status (never smoker, previous smoker, and current smoker), alcohol consumption (daily or almost daily, 1–4 times a week, 1–3 times a month, special occasions only, or never), physical activity (low, moderate, and high), fruit and vegetable intake (≥5 portions, <5 portions), salt added to food (never or rarely, sometimes, usually, and always), BMI, sleep time (<8, 8, 8–9, and >9 hours).
[c]Multivariable adjusted model 2: additionally adjusted for hypercholesterolemia (yes or no), hypertension (yes or no), diabetes (yes or no), mental health disorders (yes or no), COPD (yes or no), asthma (yes or no), atrial fibrillation (yes or no), inflammatory bowel disease (yes or no), cholelithiasis (yes or no), rheumatoid arthritis (yes or no), renal failure (yes or no), gastritis (yes or no), liver disease (yes or no), anemia (yes or no), multivitamin use (yes or no), mineral supplements intake (yes or no), medications use, including aspirin (yes or no), nonaspirin NSAIDs (yes or no), acetaminophen (yes or no), angiotensin-converting enzyme inhibitors (yes or no), angiotensin receptor blocker (yes or no), beta-blockers (yes or no), calcium channel blockers (yes or no), thiazide diuretics (yes or no), statin (yes or no), metformin (yes or no), and insulin treatment (yes or no).
[d]Multivariable adjusted model 3: additionally adjusted for general health indicator variables, including overall health rating (poor, fair, good, and excellent) and longstanding illness (yes or no).

increased risk of mortality (see Supplementary Table S1, Supplementary Digital Content 3, http://links.lww.com/AJG/C103). There was no major change in the sensitivity analyses by lagging the exposure for 4 years and restricting the participants to gastroesophageal reflux disease (see Supplementary Tables S2 and S3, Supplementary Digital Contents 4 and 5, http://links.lww.com/AJG/C104, http://links.lww.com/AJG/C105).

For individual PPIs, regular use of omeprazole, lansoprazole, esomeprazole, and other PPIs showed no associations with all-cause mortality (Figure 1). We generally found no evidence of interaction for sex, age, body mass index, smoking, physical activity, PPI indications, and regular use of nonsteroidal anti-inflammatory drugs (see Supplementary Figures S2–S8, Supplementary Digital Contents 6–12, http://links.lww.com/AJG/C106, http://links.lww.com/AJG/C107, http://links.lww.com/AJG/C108, http://links.lww.com/AJG/C109, http://links.lww.com/AJG/C110, http://links.lww.com/AJG/C111, http://links.lww.com/AJG/C112).

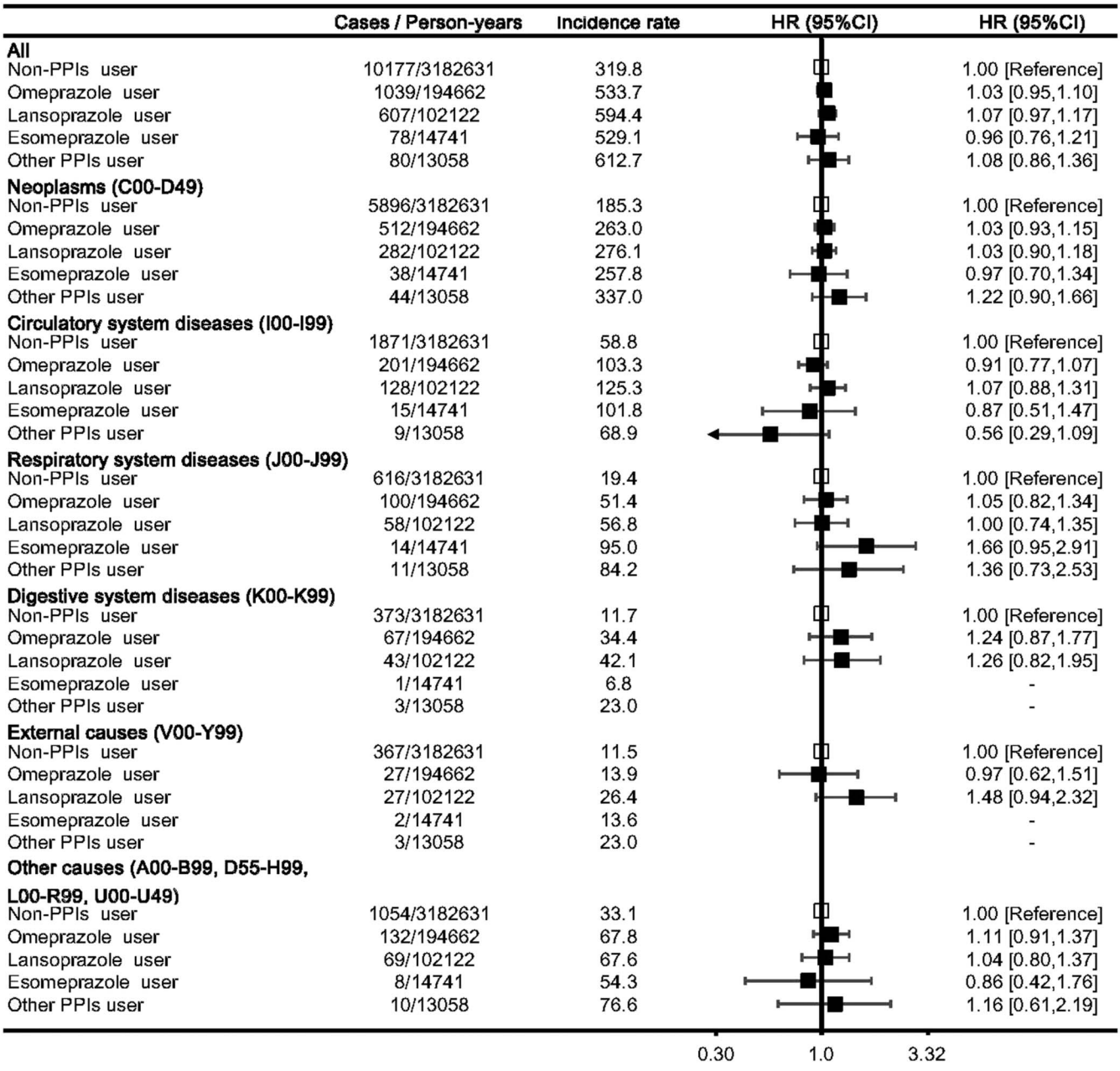

Figure 1. Risk of all-cause and cause-specific mortality by the class of proton pump inhibitors in the UK Biobank. Estimated effects were based on age, sex, and PPI indication-stratified model with adjustment for ethnicity, socioeconomic status, education level, smoking status, alcohol consumption, physical activity, fruit and vegetable intake, salt added to food, BMI, sleep time, hypercholesterolemia, hypertension, diabetes, mental health disorders, COPD, asthma, atrial fibrillation, inflammatory bowel disease, cholelithiasis, rheumatoid arthritis, renal failure, gastritis, liver disease, anemia, multivitamin use, mineral supplements intake, medications use (aspirin, nonaspirin NSAIDs, acetaminophen, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta-blockers, calcium channel blockers, thiazide diuretics, statin, metformin, and insulin treatment), and general health indicator variables, including overall health rating and longstanding illness. HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

DISCUSSION

The detailed discussion was reported in Supplementary eDiscussion (see Supplementary Digital Content 1, http://links.lww.com/AJG/C101). The findings of previous population-based cohort studies evaluating PPIs and mortality were inconsistent, showing either a positive (4,5) or a null association (6). The primary rationale for increased mortality among PPI users is that PPIs are associated with various adverse outcomes and each is independently associated with higher risk of mortality. However, this inference may not be reliable because (i) the causal relationships between PPI use and most adverse outcomes have not been established (1); (ii) even if these associations are causal, the magnitudes of effects are small (most HRs were <2), the proportion of participants that finally progress from these adverse outcomes to death would be small and require long period. Our results were in line with a recent cohort study, which suggested the association of PPIs with mortality may be due to

protopathic bias (6). The additional contributions of the present analysis included the following: (i) we evaluated cause-specific mortality and the effects of individual PPIs and (ii) we identified a number of key confounding factors, particularly overall health status and longstanding disease, which have not been controlled in most previous observational studies. For example, a single adjustment for overall health rating led to a reduction in the HRs, from 1.37 to 1.05, for all-cause mortality (magnitude of confounding = 30.5%, which was much lower than the recommended cutoff change (10%) for assessing a confounder (14)).

Our strengths included large sample size, high quality data source, adequate adjustment of confounding factors, and comparison with active control. A major limitation is potential misclassification of exposure because it was only assessed once at baseline. However, in a subset of 20,344 participants with reassessment of PPI use during 2012–13, the concordance rate was high (91.4%). Despite the large sample size, this study may not be able to test very small difference. Given the very wide overall PPI use in the population, a small risk increase may be consequential.

Overall, this large cohort found no convincing evidence of associations between regular PPI use and risk of all-cause and cause-specific mortality. In clinical practice, there is no justification to stop PPI use out of concerns of increased mortality for patients with a valid indication. The potential long-term effects other than mortality remain to be determined. Future observational studies evaluating side effects of drugs should comprehensively adjust for confounders and carefully interpret the results to avoid misleading patients or the general public.

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CONFLICTS OF INTEREST

Guarantor of the article: Jinqiu Yuan, PhD.

Specific author contributions: Qiangsheng He, MM, Bin Xia, PhD, and Wenbo Meng, MD, PhD, contributed equally to this study. M.Y., Y.P., and J.Y.: concept and design. All authors: acquisition, analysis, or interpretation of data. J.Y., M.Y., and W.M.: drafting of the article. All authors: critical revision of the article for important intellectual content. Q.H., J.Y., and B.X.: statistical analysis. M.Y., Y.P., and B.X.: obtained funding. Y.P. and J.Y.: administrative, technical, or material support. Y.P. and J.Y.: supervision.

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REFERENCES

1. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: Expert review and best practice advice from the American Gastroenterological Association. Gastroenterology 2017;152:706–15.
2. Nehra AK, Alexander JA, Loftus CG, et al. Proton pump inhibitors: Review of emerging concerns. Mayo Clin Proc 2018;93:240–6.
3. Wilson N, Gnjidic D, March L, et al. Use of PPIs are not associated with mortality in institutionalized older people. Arch Intern Med 2011;171:866; author reply 866–7.
4. Xie Y, Bowe B, Yan Y, et al. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: Cohort study. BMJ 2019;365:l1580.
5. Xie Y, Bowe B, Li T, et al. Risk of death among users of proton pump inhibitors: A longitudinal observational cohort study of United States veterans. BMJ Open 2017;7:e015735.
6. Baik SH, Fung KW, McDonald CJ. The mortality risk of proton pump inhibitors in 1.9 million US seniors: An extended Cox survival analysis. Clin Gastroenterol Hepatol 2021 [Epub ahead of print, January 13, 2021.] doi:10.1016/j.cgh.2021.01.014.
7. Maggio M, Corsonello A, Ceda GP, et al. Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients discharged from acute care hospitals. JAMA Intern Med 2013;173:518–23.
8. Dal-Paz K, Moraes-Filho JP, Navarro-Rodriguez T, et al. Low levels of adherence with proton pump inhibitor therapy contribute to therapeutic failure in gastroesophageal reflux disease. Dis Esophagus 2012;25:107–13.
9. Kurlander JE, Kennedy JK, Rubenstein JH, et al. Patients' perceptions of proton pump inhibitor risks and attempts at discontinuation: A national survey. Am J Gastroenterol 2019;114:244–9.
10. Kurlander JE, Rubenstein JH, Richardson CR, et al. Physicians' perceptions of proton pump inhibitor risks and recommendations to discontinue: A national survey. Am J Gastroenterol 2020;115:689–96.
11. Safer DJ. Overprescribed medications for US adults: Four major examples. J Clin Med Res 2019;11:617–22.
12. Sudlow C, Gallacher J, Allen N, et al. UK biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
13. UK Biobank. Protocol for a large-scale prospective epidemiological resource. (https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf). Accessed October 12, 2020.
14. LaMorte WW, Sullivan L. Confounding and effect measure modification. (https://sphweb.bumc.bu.edu/otlt/mph-modules/bs/bs704-ep713_confounding-em/bs704-ep713_confounding-em_print.html). Accessed October 25, 2020.