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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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)       |
| 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/m²                                 | 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)         |

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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 gastrointestinal reflux disease; H2RA, histamine-2 receptor antagonist; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

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 1. (continued) | Regular PPI use |
|----------------------|----------------|
| Characteristics      | No (N = 402,775) | Yes (N = 38,065) | Overall (N = 440,840) |
| 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 (%)       | 44,533 (11.1)   | 8,753 (23.0)    | 53,286 (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 (%) |
| Poor                  | 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.
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, lansopra- zole, 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).

### 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* | Hazard ratio (95% confidence interval) |
|--------------------------------|-----------|--------------|-----------------|----------------------------------------|
|                                |           |              |                 | Age, sex, and indication-stratified model | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| All                            |           |              |                 | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| 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)            |           |              |                 | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| 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) |           |              |                 | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| 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) |           |              |                 | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| 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) |           |              |                 | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| 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)      |           |              |                 | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| 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) |           |              |                 | Multivariable-adjusted model 1b | Multivariable-adjusted model 2c | Multivariable-adjusted model 3d |
| 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.

*Per 100,000 person-years.

bMultivariable-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, 8–9, and ≥9 hours).

cMultivariable-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).

dMultivariable-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).
### 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

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**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.

| Class of Proton Pump Inhibitors | Cases / Person-years | Incidence rate | HR (95%CI) | HR (95%CI) |
|--------------------------------|----------------------|---------------|------------|------------|
| All                           | 10177/3182631        | 319.8         | 1.00       | [Reference]|
| Non-PPIs user                 |                      |               |            |            |
| Omeprazole user               | 1039/194662          | 533.7         | 1.03       | [0.95,1.10]|
| Lansoprazole user             | 607/102122           | 594.4         | 1.07       | [0.97,1.17]|
| Esomeprazole user             | 78/14741             | 529.1         | 0.96       | [0.76,1.21]|
| Other PPIs user               | 80/13058             | 612.7         | 1.08       | [0.86,1.36]|

Neoplasms (C00-D49)

| Class of Proton Pump Inhibitors | Cases / Person-years | Incidence rate | HR (95%CI) | HR (95%CI) |
|--------------------------------|----------------------|---------------|------------|------------|
| Non-PPIs user                 | 5896/3182631         | 185.3         | 1.00       | [Reference]|
| Omeprazole user               | 512/194662           | 263.0         | 1.03       | [0.93,1.15]|
| Lansoprazole user             | 282/102122           | 278.1         | 1.03       | [0.90,1.18]|
| Esomeprazole user             | 38/14741             | 257.8         | 0.97       | [0.70,1.34]|
| Other PPIs user               | 44/13058             | 337.0         | 1.22       | [0.90,1.66]|

Circulatory system diseases (I00-I99)

| Class of Proton Pump Inhibitors | Cases / Person-years | Incidence rate | HR (95%CI) | HR (95%CI) |
|--------------------------------|----------------------|---------------|------------|------------|
| Non-PPIs user                 | 1871/3182631         | 58.8          | 1.00       | [Reference]|
| Omeprazole user               | 201/194662           | 103.3         | 0.91       | [0.77,1.07]|
| Lansoprazole user             | 128/102122           | 125.3         | 1.07       | [0.88,1.31]|
| Esomeprazole user             | 15/14741             | 101.8         | 0.87       | [0.51,1.47]|
| Other PPIs user               | 9/13058              | 66.9          | 0.56       | [0.29,1.09]|

Respiratory system diseases (J00-J99)

| Class of Proton Pump Inhibitors | Cases / Person-years | Incidence rate | HR (95%CI) | HR (95%CI) |
|--------------------------------|----------------------|---------------|------------|------------|
| Non-PPIs user                 | 616/3182631          | 19.4          | 1.00       | [Reference]|
| Omeprazole user               | 100/194662           | 51.4          | 1.05       | [0.82,1.34]|
| Lansoprazole user             | 58/102122            | 56.8          | 1.00       | [0.74,1.35]|
| Esomeprazole user             | 14/14741             | 95.0          | 1.66       | [0.95,2.91]|
| Other PPIs user               | 11/13058             | 84.2          | 1.36       | [0.73,2.53]|

Digestive system diseases (K00-K99)

| Class of Proton Pump Inhibitors | Cases / Person-years | Incidence rate | HR (95%CI) | HR (95%CI) |
|--------------------------------|----------------------|---------------|------------|------------|
| Non-PPIs user                 | 373/3182631          | 11.7          | 1.00       | [Reference]|
| Omeprazole user               | 67/194662            | 34.4          | 1.24       | [0.87,1.77]|
| Lansoprazole user             | 43/102122            | 42.1          | 1.26       | [0.82,1.95]|
| Esomeprazole user             | 1/14741              | 6.8           | -          | -          |
| Other PPIs user               | 3/13058              | 23.0          | -          | -          |

External causes (V00-Y99)

| Class of Proton Pump Inhibitors | Cases / Person-years | Incidence rate | HR (95%CI) | HR (95%CI) |
|--------------------------------|----------------------|---------------|------------|------------|
| Non-PPIs user                 | 367/3182631          | 11.5          | 1.00       | [Reference]|
| Omeprazole user               | 27/194662            | 13.9          | 0.97       | [0.62,1.51]|
| Lansoprazole user             | 27/102122            | 26.4          | 1.48       | [0.94,2.32]|
| Esomeprazole user             | 2/14741              | 13.6          | -          | -          |
| Other PPIs user               | 3/13058              | 23.0          | -          | -          |

Other causes (A00-B99, D55-H99, L00-R99, U00-U49)

| Class of Proton Pump Inhibitors | Cases / Person-years | Incidence rate | HR (95%CI) | HR (95%CI) |
|--------------------------------|----------------------|---------------|------------|------------|
| Non-PPIs user                 | 1054/3182631         | 33.1          | 1.00       | [Reference]|
| Omeprazole user               | 132/194662           | 67.8          | 1.11       | [0.91,1.37]|
| Lansoprazole user             | 69/102122            | 67.6          | 1.04       | [0.80,1.37]|
| Esomeprazole user             | 8/14741              | 54.3          | 0.86       | [0.42,1.76]|
| Other PPIs user               | 10/13058             | 76.6          | 1.16       | [0.61,2.19]|

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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 differences. 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
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