**Supplemental Digital Content 1**

**eMethods**

**Study population**

In 2006-2010, the UK Biobank recruited over 500,000 individuals aged 37-73 years from 21 assessment centers across England, Wales, and Scotland (1). When participants agreed to take part in the UK Biobank, they visited the closest assessment center to complete a self-administered, touch screen questionnaire and a face-to-face interview. Trained research staff undertook a range of physical measurements, including height, body weight, and blood pressure. Follow-up assessments were conducted through linkages to routinely available national datasets. The UK Biobank cohort has been approved by the North West Multi-center Research Ethics Committee, the England and Wales Patient Information Advisory Group, and the Scottish Community Health Index Advisory Group. All participants had provided written informed consent prior to data collection. In the present study, we excluded 26,820 participants with a diagnosis of cancer (except for non-melanoma skin cancer ICD-10 C44), 33,569 participants with major cardiovascular diseases (coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congestive heart failure) as these underlying diseases have a major influence on mortality. We also excluded 1,298 participants who subsequently withdrew from the UK Biobank, leaving a total of 440,840 participants for analysis (Supplementary figure S1).

**Assessment of PPI use**

PPIs have been approved for over-the-counter use in UK since 1999 (Omeprazole)(2). At baseline, regular use of PPIs was firstly assessed from participants using a touchscreen questionnaire, and then confirmed during verbal interview with a trained staff. In the touchscreen questionnaire, participants were asked “*Do you* *regularly take any prescription medications?*”. ‘Regularly’ was typically defined as most days of the week for the last 4 weeks. If participant selected ‘Yes’ or ‘Unsure’, then they would be asked by the interviewer: “*In the touch screen you said you are taking regular prescription medications. Can you now tell me what these are?*” Information about PPI use was recorded in free text. The recorded type of PPIs included omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. Doses and duration of PPI use was not collected.

**Ascertainment of outcome**

The date and cause of death were obtained from death certificates held within the National Health Service (NHS) Digital and the NHS Central Register Scotland. Detailed information about the linkage procedures can be found at UK Biobank website(3). At the time of analysis, mortality data was available up to 31 January 2018 for England and Wales and 31 December 2016 for Scotland. The outcomes of the study were all-cause mortality and cause-specific mortality, which were identified based on underlying cause of death coded based on the ICD-10 (international classification of diseases, 10th revision). Causes of death were categorized into the following categories: neoplasms (C00-D49); circulatory system diseases (I00-I99); respiratory system diseases (J00-J99); digestive system diseases (K00-K99); external causes (V00-Y99); and other causes (A00-B99, D55-H99, L00-R99, U00-U49).

**Assessment of covariates**

Covariate information were obtained at baseline. Sociodemographic factors (*age, sex, ethnicity, education, and assessment center*), lifestyle habits (*smoking status, alcohol consumption, sleep time, and dietary intake*), multivitamin use, intake of mineral supplements, and general health (*overall health rating and longstanding illness*) were self-reported. Index of multiple deprivation, a composite measure of socioeconomic status, was provided directly from the UK Biobank. Physical activity was assessed using the International Physical Activity Questionnaire - Short Form (IPAQ-SF). Current concomitant comorbidities (*hypercholesterolemia, diabetes, atrial fibrillation, mental health disorders, chronic obstructive pulmonary disease (COPD), asthma, atrial fibrillation, inflammatory bowel disease, cholelithiasis, rheumatoid arthritis, renal failure, gastritis, liver disease, anaemia,* *esophagitis/Barretts oesophagus,* *GERD, peptic ulcer, dyspepsia, and upper gastrointestinal bleeding*) were identified by combining information from these different data sources, including primary care, hospital admissions, self-report and death register. Current medication use (*aspirin, non-aspirin* *non-steroidal anti-inflammatory drugs [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], anticoagulants/antiplatelets, and insulin*) were firstly assessed based on self-reported medical history and subsequently verified by face-to-face interview. Height, weight and blood pressure were measured by trained research staff. The clinical indications for PPI use were defined as a composite of esophagitis/Barretts oesophagus, GERD, peptic ulcer, dyspepsia, and upper gastrointestinal bleeding.

**Statistical analysis**

To minimize reverse causality (disease leading to PPI use), we set a 2-year interval between the time of exposure and incident death, which provided a time window for death occurrence. 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. Cox regression models taking age as the timescale were fitted to estimate the hazard ratios (HRs) and confidence intervals (CIs). In the basic model, we stratified the analyses jointly by sex, age (37-50, 50-60, 60-70, ≥70 years) and indication for PPI use. In the multivariable-adjusted model 1, we adjusted for ethnicity, socioeconomic status, education level, smoking status, alcohol consumption, salt added to food, physical activity, fruit and vegetable intake, body mass index (BMI), sleep time, multivitamin and mineral supplements intake. We additionally adjusted for hypertension, hypercholesterolemia, mental health disorders, COPD, asthma, atrial fibrillation, inflammatory bowel disease, cholelithiasis, rheumatoid arthritis, renal failure, gastritis, liver disease, anaemia and other medications use (including aspirin, non-aspirin NSAIDs, acetaminophen, ACEIs, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics, statin, metformin and insulin treatment) in the multivariable-adjusted model 2. To address the possible confounding effect of individuals’ health status, we additionally adjusted for general health indicator variables, including overall health rating and longstanding illness in the multivariable-adjusted model 3. Proportional hazards assumption was checked using Schoenfeld’s tests and no violation was shown. For covariates with responses of ‘*do not know*’ and ‘*prefer not to answer*’, or with missing data, we included an “unknown/missing” value indicator.

To explore potential interaction effects, we undertook subgroup analyses by age, sex, BMI, smoking, physical activity, PPI indications, and regular use of NSAIDs. We performed a number of sensitivity analyses. First, we lagged the exposure for an even longer period (4 years) to minimize the effects of reverse causality. Second, to explore potential bias due to the underlying indications, we evaluated the mortality risk of PPIs using H2RA, a class of less potent acid-suppressive agents, as active control. Third, we limited the analysis to participants with GERD. All analyses were performed using SAS software, Version 9.4 (SAS Institute, Cary, North Carolina, USA).

**eDiscussion**

In this prospective analysis of 0.44 million UK residents, we observed associations between regular PPI use and risk of all-cause mortality and cause-specific mortality (neoplasms, circulatory system diseases, digestive system diseases, and other causes) in the age, gender and indication-stratified model. However, these associations attenuated to null after multivariate adjustment for confounding factors like lifestyle habits, comorbidities, and self-reported overall health status. Additional subgroup analyses, sensitivity analyses, and comparison with active control consistently showed a negative finding.

Prior epidemiological studies evaluating PPIs and mortality risk showed inconsistent findings. Prospective analyses of older adults who were discharged from acute care hospitals or the institutionalized elderly showed either a positive (4, 5) or null association (6) between PPI use and one-year mortality. In two population-based cohort studies of US veterans, Yan and colleagues found a small excess of all-cause mortality among PPI users (7, 8). In a recent cohort of 1.9 million US seniors(9), PPI use (versus no use) was associated with a 10% increased mortality risk (HR 1.10, 95% CI 1.08 to1.12) in the analysis with no lag-time; However, mortality risk was no longer associated with PPI use with a lag-time of 90 days (HR 1.01, 95% CI 0.99 to 1.02). Potential explanation for the inconsistent findings included different analysis methods and adjustment for confounders. In the present study, we lagged the exposure for 2 years and made a comprehensive adjustment for potential confounders, which in turn, minimized these biases.

In addition to the current analysis, only one study evaluated PPI and risk of cause-specific mortality (7), which showed different findings. An explanation for the inconsistency is that we adjusted more covariates and some showed confounding effects. To compare these results, we only adjusted for the covariates mentioned in the previous study (7) in an additional analysis. We observed significant associations between PPI use with all-cause cause mortality (HR 1.33, 95%CI 1.24 to 1.42) and mortality due to cardiovascular disease (HR 1.32, 95%CI 1.13 to 1.55), neoplasms (HR 1.16, 95%CI 1.05 to 1.28), respiratory system diseases (HR 1.90, 95%CI 1.51 to 2.39), and digestive system diseases (HR 1.92, 95%CI 1.34 to 2.76), suggesting the importance of adequate adjustment in observational studies of drugs (10). The additional contributions of the present analysis included: 1) We evaluated cause-specific mortality and the effects of individual PPIs; and 2) 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.

The primary rationale for increased mortality among PPI users reported in the previous studies (7, 8) 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 1) the causal relationships between PPI use and most adverse outcomes have not been established (11); 2) even if these associations are causal, the magnitudes of effects are small (most HRs were < 2), the proportion of participants that finally progress from the adverse outcomes to death would be small and require long time (e.g. fractures and chronic kidney disease), thus it is hard to directly observe an association between PPIs and mortality.

As reported in previous studies (12, 13), our analysis for the baseline characteristics confirmed that PPI users had higher rates of multiple comorbidities. These comorbidities included both indications of PPIs such as GERD, and non-PPI indications like hyperlipidemia and mental health disorders. Therefore, comorbidities are very likely to confound the relationship between PPIs and mortality. Additionally, previous studies indicated excess mortality risk due to PPI use may be confounded by unobserved patient characteristics (such as poor health literacy or adherence) (14, 15). Although previous epidemiological studies have controlled for a number of comorbidities, it is hard to control all known and unknown diseases thus, residual confounding effect cannot be fully excluded (7, 8). In the present study, we controlled for overall health rating, which is an indicator of self-perceived health status with no specific focus on any disease. Additional adjustments of overall health rating in the age, gender and indication-stratified Cox regression model led to a major reduction in the estimate effects (the HRs for all-cause mortality reduced from 1.37 to 1.05, magnitude of confounding = 30.5% ). This confirmed the confounding effect for health status according to the general recommended cut-off changes (10%) between the adjusted and unadjusted estimated effects for the assessment of a confounder (16). Similarly, adjustment for self-reported longstanding illness also demonstrate a confounding effect (the HRs for all-cause mortality reduced from 1.37 to 1.18, magnitude of confounding = 16.1%).

One of our strengths is that this study was based on a well-established prospective cohort with a comprehensive collection of data 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 number of events enabled us to get precisely estimated effects for individual class of PPIs, subgroups, and cause-specific mortality. Lastly, sensitivity analyses were robust and additional analyses taking active control, H2RA, showed stable results.

This study has its limitations. Firstly, as information about PPI use were collected only once at baseline, we were unable to investigate the effects of time varying covariates and exposures on mortality. The risk of misclassification is high in conjunction with the two years post inclusion lag-time as it may happen that exposed/non-exposed populations have changed. However, in a subset of 20,344 participants with repeated assessment of PPI use during 2012-2013, the concordance rate was high (91.4%). Secondly, the median follow-up was 5.9 years (maximum: 8.8 years), the effects of PPIs with even longer follow-up remain to be determined. Thirdly, ‘regular use’ was defined as most days of the week for the last 4 weeks in our analysis, the effect of past, ever, or even longer exposure to PPIs is still unclear. Fourthly, as an observational study, we cannot fully exclude potential confounding effect due to the indication of PPIs. However, the influence would be minimal as our analyses were based on indication-stratified model with comprehensive adjustment for comorbidities and overall health status. The consistent results of the direct comparison with H2RA and restriction of participants in GERD further strengthened our findings.Lastly, despite the large sample size, this study may not be able to test very small difference. Given the overall PPI use is very wide in population, a small risk increase may be consequential.

Overall, this large population-based cohort study found no convincing evidence of associations between regular PPI use and risk of all-cause and cause-specific mortality after adjustment for lifestyle habits, comorbidities, and personal overall health status. Prior reports of increased risk of mortality in PPI users might be due to residual confounding effects. Our results should provide robust clinical evidence regarding the benefits and harms of PPI therapy. For patients with a valid indication, there is no justification to stop PPI use out of concerns of increased mortality. 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 findings so as to avoid misleading patients or the general public.

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