**Supplemental Digital Content 5**

**Table S3.** Associations of regular use of PPI with the risk of all-causes and specific-cause mortality in participants with gastroesophageal reflux disease.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cause of death** | **Cases** | **Person-years** | **Incidence rate \*** | **Hazard Ratio [95% Confidence Interval]** | | |  |
| Age, gender and indication-stratified model | Multivariable adjusted model 1† | Multivariable adjusted model 2‡ | Multivariable adjusted model 3¶ |
| **All** |  |  |  |  |  |  |  |
| Non-regular PPI user | 217 | 47,509 | 456.8 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 592 | 93,395 | 633.9 | 1.24 [1.06,1.45] | 1.21 [1.04,1.42] | 1.17 [0.99,1.38] | 1.12 [0.95,1.33] |
| **Neoplasms (C00-D49)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 113 | 47,509 | 237.8 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 293 | 93,395 | 313.7 | 1.16 [0.93,1.44] | 1.13 [0.91,1.41] | 1.14 [0.90,1.43] | 1.13 [0.90,1.43] |
| **Circulatory system diseases (I00-I99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 48 | 47,509 | 101 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 118 | 93,395 | 126.3 | 1.13 [0.81,1.59] | 1.07 [0.77,1.50] | 0.98 [0.69,1.40] | 0.92 [0.64,1.31] |
| **Respiratory system diseases (J00-J99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 17 | 47,509 | 35.8 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 58 | 93,395 | 62.1 | 1.48 [0.86,2.55] | 1.54 [0.89,2.67] | 1.53 [0.85,2.74] | 1.35 [0.75,2.44] |
| **Digestive system diseases (K00-K99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 11 | 47,509 | 23.2 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 37 | 93,395 | 39.6 | 1.63 [0.83,3.20] | 1.68 [0.85,3.32] | 1.26 [0.61,2.61] | 1.19 [0.57,2.48] |
| **External causes (V00-Y99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 7 | 47,509 | 14.7 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 18 | 93,395 | 19.3 | 1.32 [0.55,3.19] | 1.25 [0.51,3.04] | 1.57 [0.59,4.15] | 1.64 [0.61,4.37] |
| **Other causes (A00-B99, D55-H99, L00-R99, U00-U49)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 21 | 47,509 | 44.2 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 68 | 93,395 | 72.8 | 1.49 [0.91,2.43] | 1.45 [0.89,2.38] | 1.30 [0.78,2.17] | 1.18 [0.71,1.97] |

\* Per 100 000 person years.

† Multivariable adjusted model 1: additionally adjusted for ethnicity (*white*, *other*), socioeconomic status (*index of multiple deprivation*, fifth), education level (*college or university degree*, *other*),smoking status (*never smoker*, *previous smoker*, *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*, *high*), fruit and vegetable intake (*≥5 portions*, *<5 portions*), salt added to food (*never or rarely*, *sometimes*, *usually*, *always*), BMI, sleep time (*<8 hours*, *8 hours*, *8 to 9 hours*, *>9 hours*).

‡ 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*), anaemia (*yes* or *no*), multivitamin use (*yes* or *no*), mineral supplements intake (*yes* or *no*), and medications use, including aspirin (*yes* or *no*), non-aspirin 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*), insulin treatment (*yes* or *no*).

¶ Multivariable adjusted model 3: additionally adjusted for general health indicator variables, including overall health rating (*poor*, *fair*, *good*, *excellent*) and longstanding illness (*yes* or *no*).

Abbreviation: PPI, proton pump inhibitor.