**Supplemental Digital Content 4**

**Table S2**. Associations of regular use of PPI with the risk of all-causes and specific-cause mortality after lagging the exposure for 4 years.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 | 8,105 | 1,577,935 | 513.6 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 1,318 | 147,000 | 896.6 | 1.34 [1.25,1.44] | 1.21 [1.13,1.30] | 1.13 [1.05,1.21] | 1.04 [0.97,1.11] |
| **Neoplasms (C00-D49)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 4,663 | 1,577,935 | 295.5 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 626 | 147,000 | 425.9 | 1.15 [1.05,1.27] | 1.07 [0.97,1.19] | 1.06 [0.96,1.17] | 1.02 [0.92,1.13] |
| **Circulatory system diseases (I00-I99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 1,479 | 1,577,935 | 93.7 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 256 | 147,000 | 174.1 | 1.33 [1.13,1.56] | 1.14 [0.97,1.33] | 1.02 [0.87,1.20] | 0.94 [0.80,1.10] |
| **Respiratory system diseases (J00-J99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 528 | 1,577,935 | 33.5 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 138 | 147,000 | 93.9 | 1.74 [1.38,2.20] | 1.53 [1.22,1.92] | 1.24 [0.99,1.56] | 1.02 [0.81,1.27] |
| **Digestive system diseases (K00-K99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 290 | 1,577,935 | 18.4 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 80 | 147,000 | 54.4 | 1.93 [1.34,2.76] | 1.54 [1.08,2.19] | 1.32 [0.92,1.88] | 1.15 [0.81,1.64] |
| **External causes (V00-Y99)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 263 | 1,577,935 | 16.7 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 41 | 147,000 | 27.9 | 1.63 [1.09,2.43] | 1.52 [1.02,2.26] | 1.35 [0.90,2.01] | 1.25 [0.84,1.87] |
| **Other causes (A00-B99, D55-H99, L00-R99, U00-U49)** |  |  |  |  |  |  |  |
| Non-regular PPI user | 882 | 1,577,935 | 55.9 | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPI user | 177 | 147,000 | 120.4 | 1.85 [1.53,2.24] | 1.65 [1.37,2.00] | 1.46 [1.20,1.77] | 1.20 [0.98,1.47] |

\* 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.