**Use of Proton Pump Inhibitors and Risk of Pancreatic Cancer: A Nationwide Case-Control Study Based on the French National Health Data System (SNDS)**

# SUPPLEMENTARY DATA FILES

Supplementary File S1. Presentation of the SNDS databases 2

Supplementary Table S1. List of codes used to identify exclusion criteria 4

Supplementary Table S2. List of codes used to identify medical covariates 5

Supplementary Table S3. Description of proton pump inhibitor exposure among cases and controls 13

Supplementary Table S4. Association of main risk factors with pancreatic cancer 14

Supplementary Table S5. Association between exposure to proton pump inhibitors and pancreatic cancer – Sensitivity analyses with 2-year or 4-year lag periods on PPI exposure 15

Supplementary Table S6. Association between exposure to proton pump inhibitors and pancreatic cancer among new users – Sensitivity analyses 16

Supplementary Table S7. Association between ever use of proton pump inhibitors and pancreatic cancer – Sensitivity analyses with stabilized IPTW 17

Supplementary Table S8. Association between exposure to proton pump inhibitors and pancreatic cancer, compared to exposure to histamine‐2‐receptor antagonists – Sensitivity analyses 17

eReferences 18

## Supplementary File S1. Presentation of the SNDS databases

The French National Health Data System (Système National des Données de Santé, SNDS), records detailed information on individual health insurance claims for inpatient and outpatient care, from both the SNIIRAM (Système National d’Information Inter-Régime de l’Assurance Maladie, National Health Insurance claims information system) and PMSI (Programme de Médicalisation des Systèmes d’Information, national hospital discharge database).

The database contains data about all outpatient services reimbursed by National Health Insurance, including drugs (coded according to Anatomical Therapeutic Chemical Classification System [ATC](1)), physician visits, and laboratory investigations, but does not provide information about the medical indications, which can be deduced from other data. Patients with costly chronic diseases (LTD: long-term diseases), such as cancer, are 100% reimbursed for their health expenditure, and the diagnosis is recorded (coded according to International Classification of Diseases, Tenth Revision [ICD-10](2)).

The database also contains the procedures performed during all hospital stays, and the principal (DP), related (DR), and associated (DAS) diagnoses (coded according to ICD-10). DP and DR correspond to the diseases justifying admission to hospital, and DAS are comorbidities or adverse events treated during the hospitalization. In order to be recorded as a hospitalization diagnosis in the database (DP, DR, or DAS), the diagnosis therefore had to have an impact on medical care. Procedures are coded according to the French medical classification for clinical procedures (CCAM, Classification commune des actes médicaux(3)). Drugs used during hospitalization are not available, except for certain expensive drugs (such as some types of cancer chemotherapy). Dates available for hospital stays are admission date, discharge date, and procedure date.

About 99% of the population living in France (67 million people) are covered by one of the various national health insurance scheme. Each national health insurance scheme reimburses almost all medical care at the same rate for both public and private care. Persons with limited income or LTD are 100% reimbursed.

SNDS data are commonly used for non-interventional studies in various conditions. To date, more than 400 published studies have used these databases(4). These comprehensive national databases are powerful tools to assess the prevalence of rare events. As the primary purpose of these databases is financial, any false statements constitute serious frauds, liable to legal proceedings, which also tends to ensure the accuracy of the data recorded. Furthermore, quality controls and audits are performed before transmission to National Health Insurance (CNAM, Caisse Nationale de l’Assurance Maladie), mainly for processing of aberrant or missing data.

## Supplementary Table S. List of codes used to identify exclusion criteria

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Cancer (All Causes) |
| **ICD-10 Codes** |  |
| C00-C97 | Malignant neoplasms |
| D00-D09 | In situ neoplasms |
| D37-D48 | Neoplasms of uncertain or unknown behaviour |
| Pancreatic Abnormality |
| **ICD-10 Codes** |  |
| E84 | Cystic fibrosisIncl.: mucoviscidosis |
| E89.1 | Postprocedural hypoinsulinaemiaIncl.: Postpancreatectomy hyperglycaemia |
| Q45.0 | Agenesis, aplasia and hypoplasia of pancreasCongenital absence of pancreas |
| Q45.1 | Annular pancreas |
| Q45.2 | Congenital pancreatic cyst |
| Q45.3 | Other congenital malformations of pancreas and pancreatic ductAccessory pancreasCongenital malformation of pancreas or pancreatic duct NOS |
| Z94.81 | Other transplanted organ and tissue statusPancreas |

ICD-10: International Classification of Diseases, Tenth Revision.

## Supplementary Table S. List of codes used to identify medical covariates

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Diabetes mellitus |
| **ICD-10 Codes** |  |
| E10 | Insulin-dependent diabetes mellitus |
| E11 | Non-insulin-dependent diabetes mellitus |
| E12 | Malnutrition-related diabetes mellitus |
| E13 | Other specified diabetes mellitus |
| E14 | Unspecified diabetes mellitus |
| **ATC Codes** |  |
| A10A | Insulins and analogues |
| A10B | Blood glucose lowering drugs, excl. insulins |
| Complications of diabetes mellitus |
| **ICD-10 Codes** |  |
| G59.0 | Diabetic mononeuropathy |
| G63.2 | Diabetic polyneuropathy |
| G73.0 | Myasthenic syndromes in endocrine diseasesIncl. in diabetic amyotrophy |
| G99.0 | Autonomic neuropathy in endocrine and metabolic diseasesAutonomic neuropathy in endocrine and metabolic diseasesIncl.: Diabetic autonomic neuropathy |
| H28.0 | Diabetic cataract |
| H36.0 | Diabetic retinopathy |
| I79.2 | Peripheral angiopathy in diseases classified elsewhereDiabetic peripheral angiopathy |
| L97 | Ulcer of lower limb, not elsewhere classified |
| M14.2 | Diabetic arthropathy |
| M14.6 | Neuropathic arthropathyIncl.: Diabetic neuropathic arthropathy |
| N08.3 | Glomerular disorders in diabetes mellitus |
| Morbid obesity |  |
| **ICD-10 Codes** |  |
| E65 | Localized adiposity |
| E66 | Obesity |

**Supplementary Table S2 (Continued)**

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Tobacco-related diseases or drug use |
| **ICD-10 Codes** |  |
| F17 | Mental and behavioural disorders due to use of tobacco |
| T65.2 | Toxic effect of other and unspecified substancesTobacco and nicotine |
| Z50.8 | Care involving use of other rehabilitation proceduresIncl.: Tobacco rehabilitation |
| Z58.7 | Exposure to tobacco smoke |
| Z71.6 | Tobacco abuse counselling |
| Z72.0 | Tobacco use |
| J41 | Simple and mucopurulent chronic bronchitis |
| J42 | Unspecified chronic bronchitis |
| J43 | Emphysema |
| J44 | Other chronic obstructive pulmonary disease |
| **ATC Codes** |  |
| N07BA | Drugs used in nicotine dependence |
| N06AX12 | Bupropion |
| Alcohol-related diseases or drug use |
| **ICD-10 Codes** |  |
| E24.4 | Alcohol-induced pseudo-Cushing syndrome |
| E52 | Niacin deficiencyIncl.:Pellagra (alcoholic) |
| F10 | Mental and behavioural disorders due to use of alcohol |
| G31.2 | Degeneration of nervous system due to alcohol |
| G62.1 | Alcoholic polyneuropathy |
| G72.1 | Alcoholic myopathy |
| I42.6 | Alcoholic cardiomyopathy |
| K29.2 | Alcoholic gastritis |
| K70 | Alcoholic liver disease |
| K85.2 | Alcohol-induced acute pancreatitis |
| K86.0 | Alcohol-induced chronic pancreatitis |
| R78.0 | Finding of alcohol in blood |
| T50.6 | Antidotes and chelating agents, not elsewhere classifiedAlcohol deterrents |
| T51.0 | Toxic effect of alcoholEthanol |
| T51.9 | Toxic effect of alcoholAlcohol, unspecified |
| X45 | Accidental poisoning by and exposure to alcohol |
| X65 | Intentional self-poisoning by and exposure to alcohol |
| Y15 | Poisoning by and exposure to alcohol, undetermined intent |
| Y57.3 | Complications of medical and surgical careOther and unspecified drugs and medicamentsAlcohol deterrents |
| Y90 | Evidence of alcohol involvement determined by blood alcohol level |
| Y91 | Evidence of alcohol involvement determined by level of intoxication |
| Z50.2 | Alcohol rehabilitation |
| Z71.4 | Alcohol abuse counselling and surveillance |
| Z72.1 | Alcohol use |
| **ATC Codes** | **Wording** |
| N07BB | Drugs used in alcohol dependence |

**Supplementary Table S2 (Continued)**

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Acute pancreatitis |  |
| **ICD-10 Codes** |  |
| K85 | Acute pancreatitis |
| Chronic Pancreatitis |
| **ICD-10 Codes** |  |
| K86.0 | Alcohol-induced chronic pancreatitis |
| K86.1 | Other chronic pancreatitis |
| Pancreatic cyst |  |
| K86.2 | Cyst of pancreas |
| K86.3 | Pseudocyst of pancreas |
| D13.6 | Benign neoplasm of other and ill-defined parts of digestive systemPancreas |
| D13.7 | Benign neoplasm of other and ill-defined parts of digestive systemEndocrine pancreas |
| Gallstones |  |
| **ICD-10 Codes** |  |
| K80 | Cholelithiasis |
| K81 | Cholecystitis |
| K87 | Disorders of gallbladder, biliary tract and pancreas in diseases classified elsewhere |
| **ATC Codes** |  |
| A05AA02 | Ursodeoxycholic acid |
| Hepatitis B or C |  |
| B16 | Acute hepatitis B |
| B17.1 | Acute hepatitis C |
| B18.0 | Chronic viral hepatitis B with delta-agent |
| B18.1 | Chronic viral hepatitis B without delta-agent |
| B18.2 | Chronic viral hepatitis C |
| Gastro-oesophageal reflux disease and complications |
| **ICD-10 codes** |  |
| K20 | Oesophagitis |
| K21 | Gastro-oesophageal reflux disease |
| K22.7 | Barrett oesophagus |
| K29 | Gastritis and duodenitis |
| Peptic ulcer |
| **ICD-10 codes** |  |
| K25 | Gastric ulcer |
| K26 | Duodenal ulcer |
| K27 | Peptic ulcer, site unspecified |
| K28 | Gastrojejunal ulcer |
| *Helicobacter pylori* eradication |
| **ICD-10 codes** |  |
| B98.0 | *Helicobacter pylori* |
| **ATC codes** |  |
| A02BD | Combinations for eradication of *Helicobacter pylori* |

**Supplementary Table S2 (Continued)**

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Acute myocardial infarction |
| **ICD-10 Codes** |  |
| I21 | Acute myocardial infarction |
| I22 | Subsequent myocardial infarction |
| I25.2 | Old myocardial infarction |
| Congestive heart failure |
| **ICD-10 Codes** |  |
| I09.9 | Rheumatic heart disease, unspecified |
| I11.0 | Hypertensive heart disease |
| I13.0 | Hypertensive heart and renal disease with (congestive) heart failure |
| I13.2 | Hypertensive heart and renal disease with both (congestive) heart failure and renal failure |
| I25.5 | Ischaemic cardiomyopathy |
| I42.0 | Dilated cardiomyopathy |
| I42.5  | Other restrictive cardiomyopathy |
| I42.6 | Alcoholic cardiomyopathy |
| I42.7 | Cardiomyopathy due to drugs and other external agents |
| I42.8 | Other cardiomyopathies |
| I42.9 | Cardiomyopathy, unspecified |
| I43 | Cardiomyopathy in diseases classified elsewhere |
| I50 | Heart failure |
| Peripheral vascular disease |
| **ICD-10 Codes** |  |
| I70 | Atherosclerosis of aorta |
| I71 | Aortic aneurysm and dissection |
| I73.1 | Thromboangiitis obliterans [Buerger] |
| I73.8 | Other specified peripheral vascular diseases |
| I73.9 | Peripheral vascular disease, unspecified |
| I77.1 | Stricture of artery |
| I79.0 | Aneurysm of aorta in diseases classified elsewhere |
| I79.2 | Peripheral angiopathy in diseases classified elsewhere |
| K55.1 | Chronic vascular disorders of intestine |
| K55.8 | Other vascular disorders of intestine |
| K55.9 | Vascular disorder of intestine, unspecified |
| Z95.8 | Presence of other cardiac and vascular implants and grafts |
| Z95.9 | Presence of cardiac and vascular implant and graft, unspecified |
| Cerebrovascular disease |
| **ICD-10 Codes** |  |
| G45 | Transient cerebral ischaemic attacks and related syndromes |
| G46 | Vascular syndromes of brain in cerebrovascular diseases |
| H34.0 | Retinal vascular occlusions |
| I60 | Subarachnoid haemorrhage |
| I61 | Intracerebral haemorrhage |
| I62 | Other nontraumatic intracranial haemorrhage |
| I63 | Cerebral infarction |
| I64 | Stroke, not specified as haemorrhage or infarction |
| I65 | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction |
| I66 | Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction |
| I67 | Other cerebrovascular diseases |
| I68 | Cerebrovascular disorders in diseases classified elsewhere |
| I69 | Sequelae of cerebrovascular disease |

**Supplementary Table S2 (Continued)**

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Dementia |
| **ICD-10 Codes** |  |
| F00 | Dementia in Alzheimer disease |
| F01 | Vascular dementia |
| F02 | Dementia in other diseases classified elsewhere |
| F03 | Unspecified dementia |
| F05.1 | Delirium superimposed on dementia |
| G30 | Alzheimer disease |
| G31.1 | Senile degeneration of brain, not elsewhere classified |
| **ATC Codes** |  |
| N06D |  |
| Chronic pulmonary disease |
| **ICD-10 Codes** |  |
| I27.8 | Other specified pulmonary heart diseases |
| I27.9 | Pulmonary heart disease, unspecified |
| J40 | Bronchitis, not specified as acute or chronic |
| J41 | Simple and mucopurulent chronic bronchitis |
| J42 | Unspecified chronic bronchitis |
| J43 | Emphysema |
| J44 | Other chronic obstructive pulmonary disease |
| J45 | Asthma |
| J46 | Status asthmaticus |
| J47 | Bronchiectasis |
| J60 | Coalworker pneumoconiosis |
| J61 | Pneumoconiosis due to asbestos and other mineral fibres |
| J62 | Pneumoconiosis due to dust containing silica |
| J63 | Pneumoconiosis due to other inorganic dusts |
| J64 | Unspecified pneumoconiosis |
| J65 | Pneumoconiosis associated with tuberculosis |
| J66 | Airway disease due to specific organic dust |
| J67 | Hypersensitivity pneumonitis due to organic dust |
| J68.4 | Chronic respiratory conditions due to chemicals, gases, fumes and vapours |
| J70.1 | Chronic and other pulmonary manifestations due to radiation |
| J70.3 | Chronic drug-induced interstitial lung disorders |
| **ATC codes** |  |
| R03 | Drugs for obstructive airway diseases |
| Rheumatic disease |
| **ICD-10 Codes** |  |
| M05 | Seropositive rheumatoid arthritis |
| M06 | Other rheumatoid arthritis |
| M31.5 | Giant cell arteritis with polymyalgia rheumatica |
| M32 | Systemic lupus erythematosus |
| M33 | Dermatopolymyositis |
| M34 | Systemic sclerosis |
| M35.1 | Other overlap syndromes |
| M35.3 | Polymyalgia rheumatica |
| M36.0 | Dermato(poly)myositis in neoplastic disease |

**Supplementary Table S2 (Continued)**

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Mild liver disease |
| **ICD-10 Codes** |  |
| B18 | Chronic viral hepatitis |
| K70.0 | Alcoholic fatty liver |
| K70.1 | Alcoholic hepatitis |
| K70.2 | Alcoholic fibrosis and sclerosis of liver |
| K70.3 | Alcoholic cirrhosis of liver |
| K70.9 | Alcoholic liver disease, unspecified |
| K71.3 | Toxic liver disease with chronic persistent hepatitis |
| K71.4 | Toxic liver disease with chronic lobular hepatitis |
| K71.5 | Toxic liver disease with chronic active hepatitis |
| K71.7 | Toxic liver disease with fibrosis and cirrhosis of liver |
| K73 | Chronic hepatitis, not elsewhere classified |
| K74 | Fibrosis and cirrhosis of liver |
| K76.0 | Nonalcoholic fatty liver disease [NAFLD] |
| K76.2 | Central haemorrhagic necrosis of liver |
| K76.3 | Infarction of liver |
| K76.4 | Peliosis hepatis |
| K76.8 | Other specified diseases of liver |
| K76.9 | Liver disease, unspecified |
| Z94.4 | Liver transplant status |
| Hemiplegia or paraplegia |
| **ICD-10 Codes** |  |
| G04.1 | Tropical spastic paraplegia |
| G11.4 | Hereditary spastic paraplegia |
| G80.1 | Spastic diplegic cerebral palsy |
| G80.2 | Spastic hemiplegic cerebral palsy |
| G81 | Hemiplegia |
| G82 | Paraplegia and tetraplegia |
| G83.0 | Diplegia of upper limbs |
| G83.1 | Monoplegia of lower limb |
| G83.2 | Monoplegia of upper limb |
| G83.3 | Monoplegia, unspecified |
| G83.4 | Cauda equina syndrome |
| G83.9 | Paralytic syndrome, unspecified |

**Supplementary Table S2 (Continued)**

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| Renal disease |  |
| **ICD-10 Codes** |  |
| I12.0 | Hypertensive renal disease with renal failure |
| I13.1 | Hypertensive heart and renal disease with renal failure |
| N03.2 | Chronic nephritic syndrome - Diffuse membranous glomerulonephritis |
| N03.3 | Chronic nephritic syndrome - Diffuse mesangial proliferative glomerulonephritis |
| N03.4 | Chronic nephritic syndrome - Diffuse endocapillary proliferative glomerulonephritis |
| N03.5 | Chronic nephritic syndrome - Diffuse mesangiocapillary glomerulonephritis |
| N03.6 | Chronic nephritic syndrome - Dense deposit disease |
| N03.7 | Chronic nephritic syndrome - Diffuse crescentic glomerulonephritis |
| N05.2 | Unspecified nephritic syndrome - Diffuse membranous glomerulonephritis |
| N05.3 | Unspecified nephritic syndrome - Diffuse mesangial proliferative glomerulonephritis |
| N05.4 | Unspecified nephritic syndrome - Diffuse endocapillary proliferative glomerulonephritis |
| N05.5 | Unspecified nephritic syndrome - Diffuse mesangiocapillary glomerulonephritis |
| N05.6 | Unspecified nephritic syndrome - Dense deposit disease |
| N05.7 | Unspecified nephritic syndrome - Diffuse crescentic glomerulonephritis |
| N18 | Chronic kidney disease |
| N19 | Unspecified kidney failure |
| N25.0 | Renal osteodystrophy |
| Z49.0 | Preparatory care for dialysis |
| Z49.1 | Extracorporeal dialysis |
| Z49.2 | Other dialysis |
| Z94.0 | Kidney transplant status |
| Z99.2 | Dependence on renal dialysis |
| Moderate or severe liver disease |
| **ICD-10 Codes** |  |
| I85.0 | Oesophageal varices with bleeding |
| I85.9 | Oesophageal varices without bleeding |
| I86.4 | Gastric varices |
| I98.2 | Oesophageal varices without bleeding in diseases classified elsewhere |
| K70.4 | Alcoholic hepatic failure |
| K71.1 | Toxic liver disease with hepatic necrosis |
| K72.1 | Chronic hepatic failure |
| K72.9 | Hepatic failure, unspecified |
| K76.5 | Hepatic veno-occlusive disease |
| K76.6 | Portal hypertension |
| K76.7 | Hepatorenal syndrome |

**Supplementary Table S2 (Continued)**

|  |  |
| --- | --- |
| **Codes** | **Wording** |
| HIV/AIDS |  |
| **ICD-10 Codes** |  |
| B20 | Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases |
| B21 | Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms |
| B22 | Human immunodeficiency virus [HIV] disease resulting in other specified diseases |
| B24 | Unspecified human immunodeficiency virus [HIV] disease |
| Nonsteroidal anti-inflammatory drugs (incl. low dose aspirin) |
| **ATC Codes** |  |
| M01A | Antiinflammatory and antirheumatic products, non-steroids |
| B01AC06 | Acetylsalicylic acid |
| B01AC30 | Acetylsalicylic acid, combinations |
| N02BA01 | Acetylsalicylic acid |
| N02BA51 | Acetylsalicylic acid, combinations excl. psycholeptics |
| Antihypertensive drugs |  |
| **ATC Codes** |  |
| C02AB02, C02AC01, C02AC02, C02AC05, C02AC06, C02CA01, C02CA06, C02DC01,C02LA01, C03AA01, C03AA03, C03BA04,C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03DA01, C03DB01, C03EA01, C03EA04, C07AA02, C07AA03, C07AA05, C07AA06, C07AA12, C07AA15, C07AA16, C07AA23, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB12, C07AG01, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C07FB02, C07FB03, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA08, C08CA09, C08CA11, C08CA13, C08CX01, C08DA01, C08DB01, C08GA02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA13, C09AA15, C09AA16, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09BB02, C09BB04, C09BB10, C09BX02, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DB01, C09DB02, C09DB04, C09XA02, C09XA52, C10BX03 |
| Statins |  |
| **ATC Codes** |  |
| C10AA | HMG CoA reductase inhibitors |

ICD-10: International Classification of Diseases, Tenth Revision.

ATC: Anatomical Therapeutic Chemical.

## Supplementary Table S. Description of proton pump inhibitor exposure among cases and controls

|  |  |  |
| --- | --- | --- |
|  | **Cases****N=23,321** | **Controls****N=75,937** |
| **All Proton Pump Inhibitors** |  |  |
| Ever use, n (%) |  |  |
| No | 5180 (22.2) | 18,630 (24.5) |
| Yes | 18,141 (77.8) | 57,307 (75.5) |
| Cumulative defined daily dose (cDDD) |  |  |
| Mean (SD) | 658.3±1079.1 | 560.8±1009.7 |
| n (%) |  |  |
| 0 cDDD | 5180 (22.2) | 18,630 (24.5) |
| 1-30 cDDD | 3186 (13.7) | 12,500 (16.5) |
| 31-180 cDDD | 4720 (20.2) | 16,056 (21.1) |
| 181-1080 cDDD | 5087 (21.8) | 14,578 (19.2) |
| >1080 cDDD | 5148 (22.1) | 14,173 (18.7) |
| **Omeprazole** |  |  |
| Ever use, n (%) |  |  |
| No | 11,464 (49.2) | 39,548 (52.1) |
| Yes | 11,857 (50.8) | 36,389 (47.9) |
| cDDD, Mean (SD) | 184.0±557.6 | 157.8±515.5 |
| **Esomeprazole** |  |  |
| Ever use, n (%) |  |  |
| No | 12,599 (54.0) | 45,118 (59.4) |
| Yes | 10,722 (46.0) | 30,819 (40.6) |
| cDDD, Mean (SD) | 228.0±666.3 | 191.7±621.8 |
| **Lansoprazole** |  |  |
| Ever use, n (%) |  |  |
| No | 17,035 (73.0) | 56,822 (74.8) |
| Yes | 6286 (27.0) | 19,115 (25.2) |
| cDDD, Mean (SD) | 76.9±361.6 | 69.5±338.2 |
| **Pantoprazole** |  |  |
| Ever use, n (%) |  |  |
| No | 14,654 (62.8) | 50,341 (66.3) |
| Yes | 8667 (37.2) | 25,596 (33.7) |
| cDDD, Mean (SD) | 106.8±393.3 | 85.5±348.6 |
| **Rabeprazole** |  |  |
| Ever use, n (%) |  |  |
| No | 18,930 (81.2) | 62,615 (82.5) |
| Yes | 4391 (18.8) | 13,322 (17.5) |
| cDDD, Mean (SD) | 62.7±334.2 | 56.3±305.0 |

SD, standard deviation.

## Supplementary Table S. Association of main risk factors with pancreatic cancer

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Risk factors** | **Cases****N=23,321** | **Controls****N=75,937** | **Crude Odds Ratio (95% CI)** | **Adjusted Odds Ratioa (95% CI)** |
| **History of diabetes mellitus** |  |  |  |  |
| No | 16,144 (69.2) | 62,633 (82.5) | 1.00 (Reference) | 1.00 (Reference) |
| Yes | 7177 (30.8) | 13,304 (17.5) | 2.20 (2.13-2.28) | 2.07 (1.99-2.16) |
| **History of tobacco-related diseases or drug use, n (%)** |  |  |  |  |
| No | 19,777 (84.8) | 68,264 (89.9) | 1.00 (Reference) | 1.00 (Reference) |
| Yes | 3544 (15.2) | 7673 (10.1) | 1.65 (1.58-1.73) | 1.35 (1.28-1.42) |
| **Morbid obesity, n (%)** |  |  |  |  |
| No | 20,385 (87.4) | 68,406 (90.1) | 1.00 (Reference) | 1.00 (Reference) |
| Yes | 2936 (12.6) | 7531 (9.9) | 1.34 (1.28-1.41) | 1.00 (0.95-1.06) |

CI, confidence interval.

aFinal model adjusted for deprivation index, history of diabetes mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones, hepatitis B or C, gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication, peripheral vascular disease, dementia, mild liver disease, AIDS, use of proton pump inhibitors, anti-hypertensive drugs, nonsteroidal anti-inflammatory drugs, and statin use.

## Supplementary Table S. Association between exposure to proton pump inhibitors and pancreatic cancer – Sensitivity analyses with 2-year or 4-year lag periods on PPI exposure

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cases****N=23,321** | **Controls****N=75,937** | **Crude Odds Ratio (95% CI)** | **Adjusted Odds Ratioa (95% CI)** |
| **2-year lag period on PPI exposure** |  |  |  |  |
| **Cumulative defined daily dose (DDD), n (%)** |  |  |  |  |
| 0 cDDD | 5180 (22.2) | 18,630 (24.5) | 1.00 (Reference) | 1.00 (Reference) |
| 1-30 cDDD | 3826 (16.4) | 13,625 (17.9) | 1.01 (0.97-1.06) | 1.00 (0.95-1.05) |
| 31–180 cDDD | 5446 (23.4) | 17,817 (23.5) | 1.12 (1.07-1.17) | 1.06 (1.01-1.11) |
| 181-1080 cDDD | 4963 (21.3) | 14,991 (19.7) | 1.24 (1.18-1.30) | 1.08 (1.03-1.14) |
| >1080 cDDD | 3906 (16.7) | 10,874 (14.3) | 1.37 (1.30-1.44) | 1.11 (1.05-1.19) |
| **4-year lag period on PPI exposure** |  |  |  |  |
| **Cumulative defined daily dose (DDD), n (%)** |  |  |  |  |
| 0 cDDD | 7102 (30.5) | 24,437 (32.2) | 1.00 (Reference) | 1.00 (Reference) |
| 1-30 cDDD | 4232 (18.1) | 14,542 (19.2) | 1.00 (0.96-1.05) | 0.98 (0.94-1.02) |
| 31–180 cDDD | 4910 (21.1) | 16,143 (21.3) | 1.06 (1.01-1.10) | 1.00 (0.95-1.05) |
| 181-1080 cDDD | 4423 (19.0) | 13,572 (17.9) | 1.15 (1.10-1.21) | 1.02 (0.97-1.07) |
| >1080 cDDD | 2654 (11.4) | 7243 (9.5) | 1.31 (1.24-1.39) | 1.08 (1.01-1.14) |

CI, confidence interval.

aFinal model adjusted for deprivation index, history of diabetes mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones, hepatitis B or C, gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication, peripheral vascular disease, dementia, mild liver disease, AIDS, use of anti-hypertensive drugs,nonsteroidal anti-inflammatory drugs, and statin use.

## Supplementary Table S. Association between exposure to proton pump inhibitors and pancreatic cancer among new users – Sensitivity analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Exposure to Proton Pump Inhibitors** | **Cases****N=15,529a** | **Controls****N=38,149a** | **Crude Odds Ratio (95% CI)** | **Adjusted Odds Ratiob (95% CI)** |
| **Ever use, n (%)** |  |  |  |  |
| No | 5051 (32.5) | 13,879 (36.4) | 1.00 (Reference) | 1.00 (Reference) |
| Yes | 10,478 (67.5) | 24,270 (63.6) | 1.12 (1.07-1.17) | 1.03 (0.99-1.08) |
| **Cumulative defined daily dose (cDDD), n (%)** |  |  |  |  |
| 0 cDDD | 5051 (32.5) | 13,879 (36.4) | 1.00 (Reference) | 1.00 (Reference) |
| 1-30 cDDD | 2618 (16.9) | 7673 (20.1) | 0.92 (0.87-0.97) | 0.92 (0.87-0.98) |
| 31-180 cDDD | 3359 (21.6) | 8111 (21.3) | 1.10 (1.04-1.16) | 1.05 (0.99-1.12) |
| 181-1080 cDDD | 2835 (18.3) | 5457 (14.3) | 1.36 (1.28-1.45) | 1.17 (1.09-1.25) |
| >1080 cDDD | 1666 (10.7) | 3029 (7.9) | 1.45 (1.35-1.57) | 1.16 (1.07-1.26) |

CI, confidence interval.

aStrata containing only cases or controls after restriction to new PPI users were removed.

bFinal model adjusted for deprivation index, history of diabetes mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones, hepatitis B or C, gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication, peripheral vascular disease, dementia, mild liver disease, AIDS, use of anti-hypertensive drugs, nonsteroidal anti-inflammatory drugs, and statin use.

## Supplementary Table S. Association between ever use of proton pump inhibitors and pancreatic cancer – Sensitivity analyses with stabilized IPTW

|  |  |  |
| --- | --- | --- |
|  | **Stabilized weights** |  |
| **Truncation percentiles 1-p, pa** | **Mean (SD)** | **Minimum-Maximum** | **Adjusted Odds Ratiob (95% CI)** |
| 1.0-99.0 | 1.0±0.4 | 0.4-2.5 | 1.02 (0.98-1.06) |
| 0.5-99.5 | 1.0±0.4 | 0.4-3.4 | 1.01 (0.97-1.05) |
| 0.1-99.1 | 1.0±0.6 | 0.3-10.7 | 0.97 (0.94-1.01) |

CI, confidence interval.

aWeights were truncated by resetting the value of the weights greater (lower) than the p (1-p) percentile to the value of the p (1-p) percentile.

bStabilized weights were computed from a logistic model using all cases and controls, adjusted for all covariates, except for CMUC (complementary universal health insurance, only available among individuals aged under 65 years).

## Supplementary Table S. Association between exposure to proton pump inhibitors and pancreatic cancer, compared to exposure to histamine‐2‐receptor antagonists – Sensitivity analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cases****N=17,400a** | **Controls****N=45,042a** | **Crude Odds Ratio (95% CI)** | **Adjusted Odds Ratiob (95% CI)** |
| **Exposure, n (%)** |  |  |  |  |
| H2RAs only | 61 (0.4) | 183 (0.4) | 1.00 (Reference) | 1.00 (Reference) |
| PPIs | 17,339 (99.6) | 44,859 (99.6) | 1.26 (0.93-1.69) | 1.03 (0.76-1.41) |
| **Cumulative defined daily dose (cDDD), n (%)** |  |  |  |  |
| H2RAs only | 61 (0.4) | 183 (0.4) | 1.00 (Reference) | 1.00 (Reference) |
| 1-30 cDDD | 3037 (17.5) | 9185 (20.4) | 1.01 (0.75-1.36) | 0.90 (0.66-1.22) |
| 31-180 cDDD | 4528 (26.0) | 12,378 (27.5) | 1.18 (0.88-1.59) | 1.02 (0.75-1.39) |
| >181-1080 cDDD | 4836 (27.8) | 11,687 (25.9) | 1.43 (1.06-1.92) | 1.15 (0.84-1.56) |
| >1080 cDDD | 4938 (28.4) | 11,609 (25.8) | 1.55 (1.15-2.08) | 1.15 (0.84-1.57) |

CI, confidence interval.

aStrata containing only cases or controls after restriction to PPI or H2RA ever users were removed.

bFinal model adjusted for deprivation index, history of diabetes mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones, hepatitis B or C, gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication, peripheral vascular disease, dementia, mild liver disease, AIDS, use of anti-hypertensive drugs, nonsteroidal anti-inflammatory drugs, and statin use.

## eReferences

1. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC - ATC/DDD Index [Internet]. [cited 2021 Mar 12]. Available from: https://www.whocc.no/atc\_ddd\_index/

2. World Health Organization. The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. World Health Organization; 1992.

3. Ministère de la Santé, de la Jeunesse et des Sports. Classification commune des actes médicaux. Bull Off. 2007;(2007/3 bis). [Internet]. [cited 2021 Mar 12]. Available from: https://solidarites-sante.gouv.fr/IMG/pdf/bo0703.pdf

4. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the système national d’information interrégimes de l’Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017;65 Suppl 4:S149–67.