**Appendix A – Data sources**

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and has been shown to have accurate and almost complete ascertainment of cancer cases. Cancer diagnoses are recorded according to the International Classification of Diseases, version 10 (ICD-10), and the ICD for Oncology (ICD-O-3) for topography and morphology codes.

The Danish National Prescription Registry contains data on all prescription drugs dispensed to Danish citizens since 1995. The data include the type of drug, date of dispensing, and quantity. The dosing information and the indication for prescribing are not available, and no information is available on drug use dispensed at hospital level. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the WHO, and the quantity dispensed for each prescription is given by the number and strength of the pharmaceutical entities (e.g., tablets), as well as the defined daily doses (DDD).

The Danish National Patient Register contains nationwide data on all non-psychiatric hospital admissions since 1977 and on all outpatient contacts since 1995. Discharge/contact diagnoses have been coded according to ICD-8 from 1977 to 1993 and ICD-10 since 1994.

Statistics Denmark administers registries on education and income. The Population Education Register contains information on the highest completed level of education, derived from type and duration of schooling.

The Danish Civil Registration System contains data on date of death and migration to and from Denmark, allowing unambiguous linkage between registries, extraction of population controls, and complete tracking of Danish inhabitants.

**Appendix B – Definitions (confounders and exclusions)**

|  |  |
| --- | --- |
|  |  |
| **Exclusion criteria** | ICD-10 code | ATC-code |
| Hereditary nonpolyposis colon cancer | C18.8A |  |
| Familial adenomatous polyposisNSAID use ≥ 2 prescriptions | D12.6FM01A excl. M01AX |  |
| Any cancer | Any record in the Cancer Registry (except NMSC) |
| **Confounders/Risk factors**Use of drugs (≥ 2 fillings prior to index date) |  |
| Drug | ATC-code |  |
| Aspirin | B01AC06; B01AC30; N02BA01 and N02BA51 |
| NSAIDs | M01A excl. M01AX |  |
| Menopausal Hormone Therapy | G03C G03D G03F G03HB10 |
| **Prior diagnoses (either a diagnostic code or a drug marker)**  |  |
| Disease | ICD-10 code | Drug markers |
| Diabetes type 2 | E11-E14, E145D, E891D, G590, G632, G730A, G990C, H280, H360, I792A, M142, N083, O241 | A10B (≥500DDD) |
| COPD | J40-44 | R03BB (≥500DDD) |
| Alcohol-related conditions | F10, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, R78.0, T51, Z72.1 | N07BB01, N07BB03, N07BB04 (ever use) |
| H. pylori infection | B980 | P01AB01+ J01FA09+ A02BC (ever use for the combination) |
| Chronic atrophic gastritis | K294, K295, K297 |  |
| Duodenal ulcers | K26 |  |
| Pernicious anemia**Socioeconomic status (education)** | B510 |  |
|  |  |  |
| Educational level | Duration of education |  |
| Basic | 10 years |  |
| Short/medium  | 11-13 years |  |
| Long | >13 years |  |
| Missing/unknown | - |  |
| NOTES: NMSC = Non-melanoma skin cancer; COPD = Chronic obstructive pulmonary disease; NSAID = Non-steroidal anti-inflammatory drugs |

**Appendix C**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **DBP containing drug products** | **Indication\*** | **ATC code** | **DBP amount used (mg)** | **Percentage of total DBP use** |
| Mesalazine | Inflammatory Bowel Disease | A07EC02 | 2,054,348 | 63,7% |
| Lithium | Bipolar disease | N05AN01 | 858,813 | 26,6% |
| Multienzymes (lipase, protease etc.) | Excorine pancreatic insufficiency | A09AA02 | 302,416 | 9,4% |
| Bisacodyl | Constipation | A06AB02 | 7,673 | 0,3% |
| **Total** |  |  | 3,223,250 | 100,0% |

**Table A1:** DBP-containing orally administered drugs used by the study population: ATC-codes, total amount redeemed and percentages of total use during the period 2004-2015.

\*Indication constituting the majority the utilization in Denmark.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **DEP containing drug products** | **Indication\*** | **ATC code** | **DEP amount used (mg)** | **Percentage of total DEP use** |
| Theophylline | Chronic Obstructive Lung Disease | R03DA04 | 2,054,349 | 82,9% |
| Erythromycin | Infections, acne | J01FA01 | 178,389 | 7,2% |
| Verapamil | Atrial fibrillation | C08DA01 | 99,583 | 4,0% |
| Mianserin | Depression | N06AX03 | 69,278 | 2,8% |
| Multienzymes (lipase, protease etc.) | Exocrine pancreatic insufficiency | A09AA02 | 23,790 | 1,0% |
| Galantamine | Alzheimerz disease | N06DA04 | 9,782 | 0,4% |
| Diclofenac, combinations | Mild to moderate pain | M01AB55 | 6,810 | 0,3% |
| Ibuprofen | Mild to moderate pain | M01AE01 | 5,998 | 0,2% |
| Bisacodyl | Constipation | A06AB02 | 4,788 | 0,2% |
| Diclofenac | Mild to moderate pain | M01AB05 | 2,482 | 0,1% |
| **Total** |  |  | 2,477,627 | 100,0% |

**Table A2:** DEP-containing orally administered drugs used by the study population: ATC-codes, total amount redeemed and percentages of total use during the period 2004-2015.

\*Indications constituting the majority of the utilization in Denmark.