# Supplementary Tables

**Table S1.** ICD-10 codes for standard asthma and comorbidity diagnoses.

|  |  |
| --- | --- |
| **Diagnosis** | **Standard diagnosis or diagnoses classified in (ICD-10 code)** |
| Acute lower respiratory infections | Acute lower respiratory infections (J20-J22) |
| Acute upper respiratory infections | Acute upper respiratory infections (J00-J06) |
| Allergic bronchopulmonary mycosis | Allergic bronchopulmonary mycosis (part of B49)  Allergic bronchopulmonary aspergillosis (part of B44.1) |
| Allergic conjunctivitis | Acute atopic conjunctivitis (H10.1) |
| Allergic rhinitis | Allergic rhinitis due to pollen (J30.1)  Other seasonal allergic rhinitis (J30.2)  Other allergic rhinitis (J30.3)  Allergic rhinitis, unspecified (J30.4) |
| Anaphylactic shock | Anaphylactic shock due to adverse food reaction (T78.0)  Anaphylactic shock, unspecified (T78.2) |
| Angina pectoris | Angina pectoris (I20) |
| Angle-closure glaucoma | Angle-closure glaucoma (part of H40.2) |
| Anxiety disorder | Phobic anxiety disorders (F40)  Other anxiety disorders (F41) |
| Asthma | Asthma (J45) other than the ones shown below  Allergic bronchitis (part of J45.0)  Pediatric asthmatic bronchitis (part of J45.0)  Asthmatic bronchitis (part of J45.9)  Status asthmaticus (J46) |
| Atopic dermatitis | Atopic dermatitis (L20) |
| Atrial fibrillation | Atrial fibrillation (part of I48) |
| Benign prostatic hyperplasia | Benign prostatic hyperplasia (part of N40) |
| Chronic obstructive pulmonary disease | Simple and mucopurulent chronic bronchitis (J41)  Unspecified chronic bronchitis (J42)  Emphysema (J43)  Other chronic obstructive pulmonary disease (J44) |
| Chronic sinusitis | Chronic sinusitis (J32) |
| Congestive heart failure | Hypertensive congestive heart failure (part of I11.0)  Congestive heart failure (I50.0) |
| Depression | Bipolar affective disorder (F31)  Depressive episode (F32)  Recurrent depressive disorder (F33) |
| Diabetes mellitus | Diabetes mellitus (E10-E14) |
| Dyslipidemia | Disorders of lipoprotein metabolism and other lipidemias (E78) |
| Eosinophilic granulomatosis with polyangiitis | Polyarteritis with lung involvement [Churg-Strauss], allergic granulomatous angiitis (M30.1) |
| Food allergy | Anaphylactic shock due to adverse food reaction (T78.0)  Other adverse food reactions, not elsewhere classified (T78.1) |
| Gastroesophageal reflux disease | Gastro-oesophageal reflux disease (K21) |
| Heart failure | Hypertensive heart failure (part of I11.0)  Hypertensive congestive heart failure (part of I11.0)  Heart failure (I50) |
| Hypertension | Hypertension (I10) |
| Hyperventilation | Hyperventilation (part of F45.3) |
| Hyperuricemia/Gout | Hyperuricemia (E79.0)  Gout (M10) |
| Influenza | Influenza due to identified zoonotic or pandemic influenza virus (J09)  Influenza due to identified seasonal influenza virus (J10)  Influenza, virus not identified (J11) |
| Lung cancer | Malignant neoplasm of bronchus and lung, upper lobe, bronchus or lung (C34.1)  Malignant neoplasm of bronchus and lung, middle lobe, bronchus or lung (C34.2)  Malignant neoplasm of bronchus and lung, lower lobe, bronchus or lung (C34.3)  Malignant neoplasm of bronchus and lung, overlapping lesion of bronchus and lung (C34.8)  Malignant neoplasm of bronchus and lung, bronchus or lung, unspecified (C34.9) |
| Myocardial infarction | Myocardial infarction (I21, I22) |
| Nasal polyp | Nasal polyp (J33) |
| Otitis media | Nonsuppurative otitis media (H65)  Suppurative and unspecified otitis media (H66)  Otitis media in diseases classified elsewhere (H67) |
| Pneumonia | Viral pneumonia, not elsewhere classified (J12)  Pneumonia due to Streptococcus pneumoniae (J13)  Pneumonia due to Hemophilus influenzae (J14)  Bacterial pneumonia, not elsewhere classified (J15)  Pneumonia due to other infectious organisms, not elsewhere classified (J16)  Pneumonia in diseases classified elsewhere (J17)  Pneumonia, organism unspecified (J18) |
| Pneumothorax | Pneumothorax (J93) |
| Pleurisy | Pleurisy (R09.1) |
| Pulmonary embolism | Pulmonary embolism (I26) |
| Sleep disorders | Sleep disorders (G47) |
| Valve disorder | Rheumatic mitral valve diseases (I05)  Rheumatic aortic valve diseases (I06)  Rheumatic tricuspid valve diseases (I07)  Multiple valve diseases (I08)  Nonrheumatic mitral valve disorders (I34)  Nonrheumatic aortic valve disorders (I35)  Nonrheumatic tricuspid valve disorders (I36)  Pulmonary valve disorders (I37)  Valve disorder (part of I38) |

From the WHO ICD-10 2016. [35]

ICD-10, International Statistical Classification of Diseases and Related Health Problems-10th revision; WHO, World Health Organization.

**Table S2.** Drug ATC codes.

|  |  |  |
| --- | --- | --- |
| **Classification** | **Generic name** | **ATC code** |
| Biologics | Omalizumab  Mepolizumab | R03DX05  R03DX09 |
| Cough suppressants | All drugs classified below  Cough suppressants, excl. combinations with expectorants  Cough suppressants and expectorants, combinations | R05D  R05F |
| Expectorants | All drugs classified below  Expectorants, excl. combinations with cough suppressants  Cough suppressants and expectorants, combinations | R05C  R05F |
| Inhaled corticosteroids | Salmeterol/Fluticasone propionate  Formoterol/Budesonide  Vilanterol/Fluticasone furoate  Formoterol/Fluticasone propionate  Beclometasone dipropionate  Budesonide  Fluticasone propionate  Mometasone furoate  Ciclesonide  Fluticasone furoate | R03AK06  R03AK07  R03AK10  R03AK11  R03BA01  R03BA02  R03BA05  R03BA07  R03BA08  R03BA09 |
| Inhaled long-acting muscarinic antagonists | Vilanterol/Umeclidinium bromide  Indacaterol/Glycopyrronium bromide  Olodaterol/Tiotropium bromide  Tiotropium bromide  Aclidinium bromide  Glycopyrronium bromide  Umeclidinium bromide | R03AL03  R03AL04  R03AL06  R03BB04  R03BB05  R03BB06  R03BB07 |
| Inhaled long-acting  β2-agonists | Salmeterol  Formoterol  Indacaterol  Olodaterol  Salmeterol/Fluticasone propionate  Formoterol/ Budesonide  Vilanterol/Fluticasone furoate  Formoterol/Fluticasone propionate  Vilanterol/Umeclidinium bromide  Indacaterol/Glycopyrronium bromide  Olodaterol/Tiotropium bromide | R03AC12  R03AC13  R03AC18  R03AC19  R03AK06  R03AK07  R03AK10  R03AK11  R03AL03  R03AL04  R03AL06 |
| Injectable corticosteroids | All injectable drugs classified below  Corticosteroids for systemic use, plain  Corticosteroids for systemic use, combinations | H02A  H02B |
| Injectable xanthines | All injectable drugs classified below  Xanthines | R03DA |
| Leukotriene receptor antagonists | All drugs classified below  Leukotriene receptor antagonists | R03DC |
| Macrolides (14- or 15-membered ring) | Erythromycin  Roxithromycin  Clarithromycin  Azithromycin | J01FA01  J01FA06  J01FA09  J01FA10 |
| Oral corticosteroids | All oral drugs classified below  Corticosteroids for systemic use, plain  Corticosteroids for systemic use, combinations  Chlorphenamine, combinations | H02A  H02B  R06AB54 |
| Oral long-acting β2-agonists | Procaterol  Tulobuterol  Clenbuterol  Formoterol  Mabuterol | R03CC08  R03CC11  R03CC13 |
| Oral xanthines | All oral drugs classified below  Xanthines  Xanthines, combinations | R03DA  R03DA20 |
| Other anti-allergics  (oral or inhaled) | Cromoglicic acid  Amlexanox  Seratrodast  Ozagrel hydrochloride hydrate  Pemirolast potassium  Repirinast  Suplatast tosilate  Tazanolast  Tranilast  All drugs classified below  Antihistamines for systemic use | R03BC01  R03DX01  R03DX06  R06A |
| Short-acting muscarinic antagonists | Ipratropium bromide  Oxitropium bromide  Isoproterenol sulfate/ Dexamethasone/Atropine methylbromide | R03BB01  R03BB02 |
| Short-acting β2-agonists | Isoprenaline (Isoproterenol)  Salbutamol  Fenoterol  Procaterol  Isoprenaline (Isoproterenol), combinations  Isoprenaline (Isoproterenol)  Methoxyphenamine  Salbutamol  Terbutaline  Fenoterol | R03AB02  R03AC02  R03AC04  R03AC16  R03CB51  R03CB01  R03CB02  R03CC02  R03CC03  R03CC04 |
| Transdermal long-acting β2-agonists | Tulobuterol | R03CC11 |

From the World Health Organization Collaborating Centre for Drug Statistics Methodology ATC/DDD 2018 [36].

ATC, Anatomical therapeutic chemical; DDD, defined daily doses.

**Table S3.** Ministry of Health, Labour, and Welfare codes for treatment types. [37]

|  |  |  |
| --- | --- | --- |
| **Classification (code)** | **Treatment** | **Code** |
| Guidance fee for in-home oxygen therapy (C103) | Guidance fee for in-home oxygen therapy (other) | 114003710 |
| Nebulizer (J114) | Nebulizer | 140022710 |
| Oxygen inhalation (J024) | Oxygen inhalation | 140005610 |
| Oxygen tent (J025) | Oxygen tent | 140005810 |
| Ultrasonic nebulizer (J115) | Ultrasonic nebulizer  Ultrasonic nebulizer, combined with oxygen therapy | 140022810  140022930 |

**Table S4.** Low, medium and high daily doses of inhaled corticosteroids, used for recording asthma medication use during the observation period.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Generic name** | **Formulation** | **Low  (μg/day)** | **Medium (μg/day)** | **High (μg/day)** | |
| Beclomethasone dipropionate | pMDI | 100–200 | 400 | 800 | |
| Budesonide  Budesonide/formoterol | DPI  IS  DPI | 200–400  500  320 | 800  1000  640 | 1600  2000  1280 | |
| Ciclesonide | pMDI | 100–200 | 400 | 800 | |
| Fluticasone propionate  Fluticasone propionate/salmeterol  Fluticasone propionate/formoterol | pMDI, DPI  pMDI, DPI  pMDI | 100–200  200  200 | 400  500  500 | 800  1000  1000 | |
| Fluticasone furoate/vilanterol | DPI | 100 | n.a. | 200 | |
| Mometasone furoate | DPI | 100–200 | 400 | 800 |

From the JSA 2017 guidelines and JSA 2018 guidelines [4, 5]

DPI, dry powder inhaler; IS, inhalation suspension; JSA, Japanese Society of Allergology; n.a., not applicable; pMDI, pressurized metered dose inhaler

**Table S5.** Low, medium and high doses of inhaled corticosteroids with fixed dose used for recording asthma medication use during the observation period.

|  |  |  |  |
| --- | --- | --- | --- |
| **Trade name** | **Inhalations/day** | **No. days fixed-dose ICS can be used** | **Dose** |
| Adoair 50 Aerosol 120 puffs  Adoair 125 Aerosol 120 puffs  Adoair 250 Aerosol 120 puffs | 4 | 30 | Low  Medium  High |
| Adoair 100 Diskus 28 doses  Adoair 100 Diskus 60 doses  Adoair 250 Diskus 28 doses  Adoair 250 Diskus 60 doses  Adoair 500 Diskus 28 doses  Adoair 500 Diskus 60 doses | 2 | 14  30  14  30  14  30 | Low  Low  Medium  Medium  High  High |
| Flutiform 50 Aerosol 56 puffs  Flutiform 50 Aerosol 120 puffs | 4 | 14  30 | Low  Low |
| Relvar 100 Ellipta 14 doses  Relvar 100 Ellipta 30 doses  Relvar 200 Ellipta 14 doses  Relvar 200 Ellipta 30 doses | 1 | 14  30  14  30 | Low  Low  High  High |

ICS, inhaled corticosteroids.

**Table S6.** Conversion of SABA inhalations.

|  |  |  |  |
| --- | --- | --- | --- |
| **Dosage for adult (inhalations at  a time)** | **Trade name** | **Inhalations/container** | **Converted inhalations/container** |
| 1 | Stmerin D Aerosol | 60 | 120 |
| 2 | Airomir Aerosol 100 μg | 200 | 200 |
| 2 | Berotec Metered Aerosol 100 | 200 | 200 |
| 2 | Meptin Clickhaler 10 μg | 200 | 200 |
| 2 | Meptin Air 10 μg 100 puffs | 100 | 100 |
| 2 | Meptin Swinghaler 10 μg  100 puffs | 100 | 100 |
| 2 | Sultanol Inhaler 100 μg | 200 | 200 |
| 4 | Meptin Kid Air 5 μg 100 puffs | 100 | 50 |

SABA, short-acting β2-agonist.

**Table S7.** Conversion of oral corticosteroid dose to prednisolone 1 mg equivalent used for recording asthma medication use during the observation period.

|  |  |  |
| --- | --- | --- |
| **Glucocorticoid** | **Approximate equivalent  dose (mg)** | **Dose (mg) corresponding  to prednisolone 1 mg** |
| Cortisone | 25 | 5 |
| Hydrocortisone | 20 | 4 |
| Prednisolone | 5 | 1 |
| Prednisone | 5 | 1 |
| Methylprednisolone | 4 | 0.8 |
| Triamcinolone | 4 | 0.8 |
| Dexamethasone | 0.75 | 0.15 |
| Betamethasone | 0.6–0.75 | 0.135 |

Asahi M et al, 1998 [38].

**Table S8**. Additional fee for emergency visit. [37]

|  |  |  |
| --- | --- | --- |
| **Classification** | **Additional fee** | **Code** |
| Late night | Additional fee for late night visit <first consultation fee>  Additional fee for late night visit <re-consultation fee>  Additional fee for late night visit <outpatient consultation fee> | 111000770  112001310  112006670 |
| Holiday | Additional fee for holiday visit <first consultation fee>  Additional fee for holiday visit <re-consultation fee>  Additional fee for holiday visit <outpatient consultation fee> | 111000670  112001210  112006570 |
| Medical management fee | Community cooperative consultation fee at night or on holiday  Critical care management fee  Management fee for emergency transportation at night or  on holiday | 113011610  113002610  113013810 |
| Home care | Critical care in transportation fee | 114003010 |
| Test | Additional fee for after-hour emergency in-house test | 160000210 |

**Table S9.** ICD-10 codes for standard asthma exacerbations.

|  |  |
| --- | --- |
| **Diagnosis** | **Standard diagnosis or diagnoses classified in (ICD-10 code)** |
| Acute respiratory failure | Acute respiratory failure (J96.0) |
| Asthmatic attack | Status asthmaticus (J46) |
| Cyanosis | Cyanosis (R23.0) |
| Hypercapnia | Hypercapnia (part of R06.8) |
| Hypoxemia | Hypoxemia (part of R09.0) |
| Paroxysmal dyspnea | Paroxysmal dyspnea (part of R06.0)  Dyspnea attack (part of R06.0) |
| Respiratory arrest | Respiratory arrest (R09.2) |

From the WHO ICD-10 2016 [35].

ICD-10, International Statistical Classification of Diseases and Related Health Problems-10th revision; WHO, World Health Organization.

**Table S10.** Database population in 2015, 2016, and 2017.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Year** | **2015** | | **2016** | | **2017** | |
| Health insurance society members joined throughout the year | 2,637,964 | | 3,339,495 | | 3,497,886 | |
| Over 15 years of age | 2,052,951 | | 2,634,495 | | 2,763,528 | |
| Asthma diagnosis (≥2 times) | 89,147 | | 123,132 | | 114,575 | |
| Asthma diagnosis (≥4 times) | 51,844 | | 72,581 | | 67,319 | |
|  | **No**  **(asthma only)** | **Yes  (ACO)** | **No**  **(asthma only)** | **Yes  (ACO)** | **No**  **(asthma only)** | **Yes (ACO)** | |
|  |  |  |  |  |  | |
| COPD\* diagnosis (≥2 times) | 46,194 | 5650 | 64,259 | 8322 | 59,507 | 7812 | |
| ICS prescription (including combination) | 26,546 | 3669 | 36,414 | 5400 | 31,891 | 4996 | |
| ICS/LABA prescription (combination) | 22,377 | 3164 | 31,184 | 4728 | 27,471 | 4402 | |
| Triple therapy prescription† | 144 | 413 | 326 | 579 | 538 | 544 | |

\*Including chronic bronchitis and pulmonary emphysema; †ICS/LABA combination and tiotropium prescribed on the same day.

ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting β2-agonists.

**Table S11.** Additional patient characteristics

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Comorbid COPD  cohort** | | **Asthma only** | | | **ACO** | | |
|  | | | **ICS/LABA**  **(n=1321)** | **Triple**  **(n=225)** | | **ICS/LABA**  **(n=100)** | **Triple**  **(n=99)** |
| Long-term management  treatment  (60 days prior to  index date) | Transdermal LABA, n (%) | | 91 (6.9) | 18 (8.0) | | 8 (8.0) | 9 (9.1) |
| Oral LABA, n (%) | | 37 (2.8) | 6 (2.7) | | 2 (2.0) | 3 (3.0) |
| Long-term macrolides, n (%) | | 29 (2.2) | 9 (4.0) | | 5 (5.0) | 8 (8.1) |
| Home oxygen therapy, n (%) | | 7 (0.5) | 5 (2.2) | | 1 (1.0) | 5 (5.1) |
| Exacerbation/symptomatic treatment  (1 year prior to index date) | Number of SABA inhalations\*, mean±SD | | 93.6±311.9 | 264.4±760.8 | | 96.2±269.3 | 194.1±364.6 |
| Oral SABA, n (%) | | 8 (0.6) | 1 (0.4) | | 1 (1.0) | 1 (1.0) |
| Inj. SABA, n (%) | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) |
| Total OCS dose (mg prednisolone equivalent), mean±SD | | 54.9±228.7 | 276.3±631.4 | | 70.9±250.8 | 365.9±906.7 |
| Cough suppressants, n (%) | | 742 (56.2) | 123 (54.7) | | 57 (57.0) | 60 (60.6) |
| SAMA, n (%) | | 4 (0.3) | 1 (0.4) | | 2 (2.0) | 1 (1.0) |
| Oxygen, n (%) | | 24 (1.8) | 13 (5.8) | | 4 (4.0) | 8 (8.1) |
| Inj. adrenaline, n (%) | | 24 (1.8) | 7 (3.1) | | 1 (1.0) | 5 (5.1) |
| Common comorbidities‡ (1 year prior to index date) | ABPM, n (%) | | 1 (0.1) | 0 (0.0) | | 0 (0.0) | 0 (0.0) |
| Anaphylactic shock, n (%) | | 3 (0.2) | 1 (0.4) | | 1 (1.0) | 0 (0.0) |
| Angina pectoris, n (%) | | 30 (2.3) | 7 (3.1) | | 3 (3.0) | 5 (5.1) |
| Angle closure glaucoma, n (%) | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) |
| Atrial fibrillation, n (%) | | 15 (1.1) | 3 (1.3) | | 0 (0.0) | 3 (3.0) |
| BPH†, n (%) | | 15 (2.5) | 6 (5.7) | | 1 (2.0) | 5 (8.8) |
| Diabetes mellitus, n (%) | | 129 (9.8) | 24 (10.7) | | 15 (15.0) | 24 (24.4) |
| Dyslipidemia, n (%) | | 256 (19.4) | 47 (21.0) | | 38 (38.0) | 38 (38.4) |
| EGPA, n (%) | | 2 (0.2) | 0 (0.0) | | 0 (0.0) | 1 (1.0) |
| Food allergy, n (%) | | 4 (0.3) | 2 (0.9) | | 0 (0.0) | 2 (2.0) |
| Hypertension, n (%) | | 228 (17.3) | 50 (22.2) | | 31 (31.0) | 31 (31.3) |
| Hyperuricemia/Gout, n (%) | | 92 (7.0) | 23 (10.2) | | 16 (16.0) | 14 (14.1) |
| Hyperventilation, n (%) | | 4 (0.3) | 1 (0.4) | | 1 (1.0) | 0 (0.0) |
| Lung cancer, n (%) | | 2 (0.2) | 1 (0.4) | | 0 (0.0) | 1 (1.0) |
| Myocardial infarction, n (%) | | 3 (0.2) | 0 (0.0) | | 0 (0.0) | 0 (0.0) |
| Nasal polyps, n (%) | | 11 (0.8) | 2 (0.9) | | 0 (0.0) | 0 (0.0) |
| Pleurisy, n (%) | | 2 (0.2) | 1 (0.4) | | 0 (0.0) | 1 (1.0) |
| Pneumothorax, n (%) | | 1 (0.1) | 0 (0.0) | | 0 (0.0) | 1 (1.0) |
| Pulmonary embolism, n (%) | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) |
| Valve disorder, n (%) | | 14 (1.1) | 1 (0.4) | | 3 (3.0) | 0 (0.0) |

\*Excluding budesonide/formoterol users; †excluding women; ‡related to asthma or allergy, respiratory symptoms, tiotropium contraindication and other.

ABPM, allergic bronchopulmonary mycosis; ACO, asthma-COPD overlap; BPH, benign prostatic hyperplasia; COPD, chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis; ICS, inhaled corticosteroids; Inj., injectable; LABA, long-acting β2-agonist; OCS, oral corticosteroids; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonists; SD, standard deviation.

**Table S12.** Additional medication use 1 year before and after index date.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Comorbid COPD** | **Asthma only (n=225)** | | **ACO (n=99)** | |
| **observation period** | **Before index** | **After index** | **Before index** | **After index** |
| Number of SABA inhalations\*, (mean±SD) | 264.4±760.8 | 246.2±727.1 | 194.1±364.6 | 149.0±402.6 |
| Oral SABA, n (%) | 1 (0.4) | 1 (0.4) | 1 (1.0) | 1 (1.0) |
| Inj. SABA, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Total OCS dose, (mg prednisolone equivalent) (mean±SD) | 276.3±631.4 | 305.9±767.9 | 365.9±906.7 | 415.9±1,231.9 |
| Cough suppressants, n (%) | 123 (54.7) | 100 (44.4) | 60 (60.6) | 44 (44.4) |
| SAMA, n (%) | 1 (0.4) | 0 (0.0) | 1 (1.0) | 0 (0.0) |
| Oxygen, n (%) | 13 (5.8) | 16 (7.1) | 8 (8.1) | 7 (7.1) |
| Inj. Adrenaline, n (%) | 7 (3.1) | 5 (2.2) | 5 (5.1) | 4 (4.0) |

\*Excluding budesonide/formoterol users.

ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; Inj., Injectable; OCS, oral corticosteroids; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

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