

SUPPLEMENTARY DATA

Suppl. Table 1. Chronic respiratory disease ICD-9 codes resulting in patient exclusion

Disease Category	ICD-9 Codes				
Asthma+COPD	49320	49321	49322		
COPD	490	49122	4940	49120	4928
	4910	4918	4941	49121	5181
	4911	4919	496	4920	5182
Other chronic lower respiratory diseases	01000	01191	01381	01611	01751
	01001	01192	01382	01612	01752
	01002	01193	01383	01613	01753
	01003	01194	01384	01614	01754
	01004	01195	01385	01615	01755
	01005	01196	01386	01616	01756
	01006	01200	01390	01620	01760
	01010	01201	01391	01621	01761
	01011	01202	01392	01622	01762
	01012	01203	01393	01623	01763
	01013	01204	01394	01624	01764
	01014	01205	01395	01625	01765
	01015	01206	01396	01626	01766
	01016	01210	01400	01630	01770
	01080	01211	01401	01631	01771
	01081	01212	01402	01632	01772
	01082	01213	01403	01633	01773
	01083	01214	01404	01634	01774
	01084	01215	01405	01635	01775
	01085	01216	01406	01636	01776
	01086	01220	01480	01640	01780
	01090	01221	01481	01641	01781
	01091	01222	01482	01642	01782
	01092	01223	01483	01643	01783
	01093	01224	01484	01644	01784
	01094	01225	01485	01645	01785
	01095	01226	01486	01646	01786
	01096	01230	01500	01650	01790
	01100	01231	01501	01651	01791
	01101	01232	01502	01652	01792
	01102	01233	01503	01653	01793
	01103	01234	01504	01654	01794
	01104	01235	01505	01655	01795
	01105	01236	01506	01656	01796
	01106	01280	01510	01660	01800
	01110	01281	01511	01661	01801
	01111	01282	01512	01662	01802
	01112	01283	01513	01663	01803
	01113	01284	01514	01664	01804
	01114	01285	01515	01665	01805
01115	01286	01516	01666	01806	
01116	01300	01520	01670	01880	
01120	01301	01521	01671	01881	
01121	01302	01522	01672	01882	
01122	01303	01523	01673	01883	

Disease Category	ICD-9 Codes				
	01123	01304	01524	01674	01884
	01124	01305	01525	01675	01885
	01125	01306	01526	01676	01886
	01126	01310	01550	01690	01890
	01130	01311	01551	01691	01891
	01131	01312	01552	01692	01892
	01132	01313	01553	01693	01893
	01133	01314	01554	01694	01894
	01134	01315	01555	01695	01895
	01135	01316	01556	01696	01896
	01136	01320	01560	01700	5110
	01140	01321	01561	01701	5111
	01141	01322	01562	01702	4950
	01142	01323	01563	01703	4951
	01143	01324	01564	01704	4952
	01144	01325	01565	01705	4953
	01145	01326	01566	01706	4954
	01146	01330	01570	01710	4955
	01150	01331	01571	01711	4956
	01151	01332	01572	01712	4957
	01152	01333	01573	01713	4958
	01153	01334	01574	01714	4959
	01154	01335	01575	01715	4760
	01155	01336	01576	01716	4761
	01156	01340	01580	01720	500
	01160	01341	01581	01721	501
	01161	01342	01582	01722	502
	01162	01343	01583	01723	503
	01163	01344	01584	01724	504
	01164	01345	01585	01725	505
	01165	01346	01586	01726	5061
	01166	01350	01590	01730	5062
	01170	01351	01591	01731	5063
	01171	01352	01592	01732	5064
	01172	01353	01593	01733	5069
	01173	01354	01594	01734	5070
	01174	01355	01595	01735	5071
	01175	01356	01596	01736	5078
	01176	01360	01600	01740	5080
	01180	01361	01601	01741	5081
	01181	01362	01602	01742	5082
	01182	01363	01603	01743	5088
	01183	01364	01604	01744	5089
	01184	01365	01605	01745	515
	01185	01366	01606	01746	51282
	01186	01380	01610	01750	51283
	01190	5172	5178	51883	51884

Suppl. Table 2. Asthma-related ICD-9 codes to identify asthma exacerbations

Category	ICD-9 Codes				
Asthma	49300	49311	49390	49310	49392
	49301	49312	49391	49381	49382
	49302	49310			
Other non-chronic lower respiratory diseases	5100	51633	5185	5160	5193
	5109	51634	51851	5161	5194
	5130	51635	51852	5162	5198
	5131	51636	51853	5163	51902
	5120	51637	5186	51630	51909
	5121	5164	5187	51631	51911
	5122	5165	51881	51632	51919
	5128	51661	51882	5199	5171
	51281	51662	51889	51669	5180
	51284	51663	51900	5168	5183
	51289	51664	51901	5169	5184
LRTI pneumonia	0330	4821	48284	4803	48242
	0331	4822	48289	4808	48249
	0338	48230	4829	4809	48281
	0339	48231	4830	481	48282
	0415	48232	4831	4820	48283
	4800	48239	4838	486	4847
	4801	48240	4841	4845	4848
	4802	48241	4843	4846	485
LRTI influenza	4870	48801	48812	488	4881
	4871	48802	48819	4880	48811
	4878	48809	48881	48882	48889
LRTI bronchitis and bronchiolitis	4660	46611	46619	5060	
LRTI other	1363	5119	78609	46421	78604
	3061	78600	7862	5118	78605
	46400	78601	7863	51181	78606
	46401	78602	78630	51189	78607
	46420	78603	78631	79539	78639
	7864	7867	7869		

LRTI, lower respiratory tract infection

Suppl. Table 3. Respiratory investigation procedure codes to identify asthma exacerbations

Procedure	Code	Type of Code
Chest X-ray	71010	CPT-4
Chest X-ray	71015	CPT-4
Chest X-ray	71020	CPT-4
Chest X-ray	71021	CPT-4
Chest X-ray	71022	CPT-4
Chest X-ray and fluoroscopy	71023	CPT-4
Chest X-ray	71030	CPT-4
Chest X-ray and fluoroscopy	71034	CPT-4
Chest X-ray	71035	CPT-4
Contrast X-ray of bronchi	71040	CPT-4
Contrast X-ray of bronchi	71060	CPT-4
X-ray exam of ribs/chest	71101	CPT-4
X-ray exam of ribs/chest	71111	CPT-4
MRI chest without dye	71550	CPT-4
MRI chest with dye	71551	CPT-4
MRI chest without & with dye	71552	CPT-4
MRI ANGIO chest with or without dye	71555	CPT-4
Plain radiography/thoracic aorta	B300	ICD10
Plain radiography of thoracic aorta	B300ZZZ	ICD10
Plain radiography respiratory sys	BB0	ICD10
Plain radiography/upper airways	BB0D	ICD10
Plain radiography of upper airways	BB0DZZZ	ICD10
Plain radiography/thoracic discs	BR02	ICD10
Plain radiography of thoracic discs	BR02ZZZ	ICD10
Plain radiography/thoracic spine	BR07	ICD10
Plain radiography of thoracic spine	BR07ZZZ	ICD10
Plain radiography/chest	BW03	ICD10
Plain radiography of chest	BW03ZZZ	ICD10
CT thorax without dye	71250	CPT-4
CT thorax with dye	71260	CPT-4
CT thorax without & with dye	71270	CPT-4
CT angiography, chest	71275	CPT-4
CT chest spine without dye	72128	CPT-4
CT chest spine with dye	72129	CPT-4
CT chest spine without & with dye	72130	CPT-4
CT scan/thoracic aorta	B320	ICD10
CT scan THOR aorta HI OSMLR CONTRST	B3200ZZ	ICD10
CT scan THOR aorta OTH CONTRST	B320YZZ	ICD10
CT scan thoracic aorta IV OPT COH	B320Z2Z	ICD10
CT scan of thoracic aorta	B320ZZZ	ICD10
CT scan/trachea/airways	BB2F	ICD10
CT TR/airways HI OSM CONT UN/ENHNCD	BB2F00Z	ICD10
CT scan TR/airways HI OSMLR CONTRST	BB2F0ZZ	ICD10
CT TR/airways L OSM CONT UN/ENHNCD	BB2F10Z	ICD10
CT scan TR/airways L OSMLR CONTRST	BB2F1ZZ	ICD10
CT TRACH/airways OTH CONT UN/ENHNCD	BB2FY0Z	ICD10
CT scan TR/airways OTH CONTRST	BB2FYZZ	ICD10
CT scan of trachea/airways	BB2FZZZ	ICD10
CT scan/thorax	BP2W	ICD10
CT scan THOR HI osmolar CONTRST	BP2W0ZZ	ICD10
CT scan THOR LOW osmolar CONTRST	BP2W1ZZ	ICD10

Procedure	Code	Type of Code
CT scan thorax other contrast	BP2WYZZ	ICD10
CT scan/thoracic spine	BR27	ICD10
CT scan of thoracic spine	BR27ZZZ	ICD10
CT scan/chest & abdomen	BW24	ICD10
CT scan chest ABD OTH CONTRST	BW24YZZ	ICD10
CT scan of chest & abdomen	BW24ZZZ	ICD10
CT scan/chest abdomen & pelvis	BW25	ICD10
CT scan chest abdomen & pelvis	BW25ZZZ	ICD10
Other X-ray of thorax	874	ICD-9
CAT of thorax	8741	ICD-9
Routine chest x-ray so described	8744	ICD-9
Other chest X-ray	8749	ICD-9
Soft tissue X-ray of thorax	873	ICD-9
Endotracheal bronchogram	8731	ICD-9
Other contrast bronchogram	8732	ICD-9
Mediastinal pneumogram	8733	ICD-9
Sinogram of chest wall	8738	ICD-9
Other soft tissue X-ray chest wall	8739	ICD-9
Diagnostic procedures lung & bronchus	332	ICD-9
Thoracoscopic lung biopsy	3320	ICD-9
Bronchoscopy thru artificial stoma	3321	ICD-9
Fiber-optic bronchoscopy	3322	ICD-9
Other bronchoscopy	3323	ICD-9
Closed biopsy of bronchus	3324	ICD-9
Open biopsy of bronchus	3325	ICD-9
Closed biopsy of lung	3326	ICD-9
Closed endoscopic biopsy of lung	3327	ICD-9
Open biopsy of lung	3328	ICD-9
Other diagnostic PROC lung/bronchus	3329	ICD-9

Suppl. Table 4. Baseline demographic, clinical characteristics, and concomitant medications for the unmatched cohorts.

Measure		Unmatched Cohorts		P-value ^b
		Budesonide Comparator (n=4236)	Budesonide Reference (n=17,393) ^a	
Year of index prescription date	Median (IQR)	2010 (2009, 2011)	2009 (2009, 2010)	<0.001 ^c
Age at index prescription date (years)	Median (IQR)	4 (2, 6)	6 (4, 11)	<0.001 ^c
Distribution of patients among age categories, n (%)	Pediatric (0-11 y)	3893 (91.9)	13,146 (75.6)	<0.001
	Adults (12+ y)	343 (8.1)	4247 (24.4)	
Gender, n (%)	Male	2589 (61.1)	10,560 (60.7)	0.604
Patients with rhinitis diagnosis ^d , n (%)	Yes	3168 (74.8)	14,414 (82.9)	<0.001
Patients with rhinitis diagnosis and/or received nasal spray ^d , n (%)	Yes	3229 (76.2)	15,006 (86.3)	<0.001
Patients with GERD diagnosis ^d , n (%)	Yes	896 (21.2)	6527 (37.5)	<0.001
Patients with oral thrush (both diagnosis and received treatment) ^d , n (%)	Yes	8 (0.2)	143 (0.8)	<0.001
Patients who received paracetamol prescriptions, n (%)	Yes	332 (7.8)	3746 (21.5)	<0.001
Distribution of patients among CCI score categories ^e , n (%)	0	1293 (30.5)	2378 (13.7)	<0.001
	1-4	2786 (65.8)	12,524 (72.0)	
	≥5	157 (3.7)	2488 (14.3)	
SABA inhalers daily dose (µg) in the year before index prescription date ^f , categorized, n (%)	0	3256 (76.9)	11,053 (63.5)	<0.001
	1-100	810 (19.1)	4382 (25.2)	
	101-200	30 (0.7)	403 (2.3)	
	201-400	77 (1.8)	759 (4.4)	
	≥401	63 (1.5)	796 (4.6)	
Prescriptions for acute courses of oral corticosteroids in the year before index prescription date, ^g categorized, n (%)	0	3858 (91.1)	13,720 (78.9)	<0.001
	1	215 (5.1)	1730 (9.9)	
	2	85 (2.0)	728 (4.2)	
	≥3	78 (1.8)	1215 (7.0)	
Baseline ICS inhalers daily dose (µg) ^f , n (%)	0	3889 (91.8)	14,806 (85.1)	<0.001
	>1-100	323 (7.6)	2062 (11.9)	
	101-200	18 (0.4)	293 (1.7)	
	201-400	5 (0.1)	154 (0.9)	
	≥401	1 (0)	77 (0.4)	

Abbreviations: CCI, Charlson Comorbidity Index; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IQR, interquartile range; N/A, not available; SABA, short-acting β₂-agonist, Y, year.

^aPatients may be included more than once in the budesonide reference continuation patient group if their index prescription date satisfied the criterion of 2 years of continuous data (1 year before and 1 year after the index prescription date). Number of unique participants in the budesonide reference cohort is 8780.

^bP-value based on Chi-square test.

^cP-value based on Mann-Whitney test.

^dThrough GP visits in the study period (2008-2012). ICD-9 codes used for comorbidities: rhinitis, 472.0 or 477; GERD, 530.81; oral thrush, 1120.

^eCalculated using the Charlson Comorbidity Index (using ICD-9 codes) over the 1-year prior to (and including) prescription date.

^fDaily dose calculated as: (count of inhalers * doses in pack) / 365) *μg strength.

^gAll courses where dosing instructions suggest exacerbation treatment (eg, 6000, 5000, 4000, 3000, 2000, 1000 reducing, or 30000 μg as directed) and/or all courses unlikely to be maintenance therapy, ie, with no dosing instructions but recorded within a ±5-day window from a lower respiratory event.

Suppl. Table 5. Baseline asthma control in the unmatched cohorts.

Measure	Unmatched Cohorts		P-value ^b
	Budesonide Comparator (n=4236)	Budesonide Reference (n=17,393) ^a	
Risk-domain asthma control ^c in the year prior to (and including) the index prescription date, n (%)			<0.001
Controlled	1254 (29.6)	3987 (22.9)	
Uncontrolled	2982 (70.4)	13,406 (77.1)	
Overall asthma control ^d in the year prior to (and including) the index prescription date, n (%)			<0.001
Controlled	1187 (28.0)	3538 (20.3)	
Uncontrolled	3049 (72.0)	13,855 (79.7)	
Number of asthma-related hospitalizations ^e in the year prior to (and including) the index prescription date, n (%)			<0.001
None	3056 (72.1)	12,239 (70.40)	
1	812 (19.2)	3134 (18.0)	
2	257 (6.1)	1104 (6.3)	
≥3	111 (2.6)	916 (5.3)	
Number of asthma ATS/ERS exacerbations ^f , n (%)			<0.001
None	3044 (71.9)	10,914 (62.7)	
1	821 (19.4)	3663 (21.1)	
2-3	312 (7.4)	1921 (11.0)	
≥4	59 (1.4)	895 (5.1)	
Number of asthma “clinical” exacerbations ^g , n (%)			<0.001
None	1254 (29.6)	3987 (22.9)	
1	1274 (30.1)	4425 (25.4)	
2-3	1315 (31.0)	5503 (31.6)	
≥4	393 (9.3)	3478 (20.0)	

Abbreviations: ATS/ERS, American Thoracic Society/European Respiratory Society.

^aPatients may be included more than once in the budesonide reference continuation patient group if their index prescription date satisfied the criterion of 2 years of continuous data (1 year before and 1 year after the index prescription date). Number of unique participants in the budesonide reference cohort is 8780.

^bP-value based on Chi-square test.

^cRisk-domain asthma control defined as the absence of asthma clinical exacerbations and outpatient department attendances.

^dOverall asthma control defined as risk-domain asthma control and average daily dose of ≤180 µg albuterol.

^eAsthma-related hospitalizations include asthma-related emergency department attendance or inpatient admissions (diagnosis and procedure codes shown in Supplemental Tables 2 and 3).

^fATS/ERS exacerbation includes asthma-related emergency department attendance or inpatient admissions or prescription for an acute course of oral corticosteroids from a lower respiratory event (diagnosis and procedure codes shown in Supplemental Tables 2 and 3).

^gClinical exacerbation includes ATS/ERS definition or prescription for antibiotics from a lower respiratory event.

Suppl. Table 6. Adverse events by system organ class at baseline in the unmatched cohorts.

AEs	Unmatched Cohorts		
	Budesonide Comparator (n=4236)	Budesonide Reference (n=17,393) ^a	<i>P</i> - value ^b
Infections and infestations, n (%) (candidiasis of the mouth and throat)			0.572
None	4231 (99.9)	17,366 (99.8)	
1	0	0	
≥2	5 (0.1)	27 (0.2)	
Immune system disorder, n (%) (cutaneous hypersensitivity reactions, angiodema, anaphylactic reactions)			NA
None	4236 (100)	17,393 (100)	
≥1	0	0	
Endocrine disorders, n (%) (adrenal suppression, growth retardation in children)			NA
None	4236 (100)	17,393 (100)	
≥1	0	0	
Metabolism and nutrition disorders, n (%) (hypokalemia, hyperglycemia)			NA
None	4236 (100)	17,393 (100)	
≥1	0	0	
Psychiatric disorders, n (%) (anxiety, insomnia, behavioral changes, depression, aggression, hyperactivity in children)			NA
None	4236 (100)	17,393 (100)	
≥1	0	0	
Eye disorders, n (%) (cataract, glaucoma)			NA
None	4236 (100)	17,393 (100)	
≥1	0	0	
Respiratory, thoracic, and mediastinal disorders, n (%) (throat irritation, hoarseness/dysphonia, brochospasm/paradoxical bronchospasm)			NA
None	4236 (100)	17,393 (100)	
≥1	0	0	
Skin and subcutaneous tissue disorders, n (%) (bruising)			NA
None	4236 (100)	17,393 (100)	
≥1	0	0	

Abbreviations: AEs, adverse events.

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^b*P*-value based on Chi-square test.