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1. Asthma-related medications per Categories, Active ingredients, Anatomical Therapeutic Chemical (ATC) codes and Drug Identification Numbers (DIN) selected in the PharmaNet database

All medications are used in calculating the number of asthma-related dispensations as a measure of asthma severity; but only a subset of the list is used for the case definition (refer to the right-most column)

Medication categories	Active ingredient(s)	ATC	DIN	Used in case definition?
Used in the 'narrow definition' of resource use (short list), also used for case-definition of asthma (see text)				
Inhaled corticosteroids (ICS)	Beclomethasone	R03BA01	2242030, 2242029, 374407, 828521, 828548, 872334, 893633, 897353, 1949993, 1950002, 2079976, 2213710, 2213729, 2215039, 2215047, 2215055, 2216531	Y
	Budesonide	R03BA02	2229099, 1978918, 1978926, 852074, 851752, 851760	Y
	Fluticasone	R03BA05	2237247, 2237246, 2237245, 2237244, 2244293, 2244292, 2244291, 2174731, 2174758, 2174766, 2174774, 2213583, 2213591, 2213605, 2213613	Y
	Ciclesonide	R03BA08	2285614, 2285606, 2303671	Y
Short-acting beta-agonists (SABA)	Salbutamol	R03AC02	790419, 812463, 832758, 832766, 851841, 860808, 867179, 897345, 1926934, 1938851, 1938878, 1945203, 1947222, 1986864, 2022125, 2046741, 2048760, 2069571, 2084333, 2148617, 2154412, 2173360, 2208229, 2208237, 2208245 2212315, 2212323, 2213400, 2213419, 2213427, 2213478, 2213486, 2214997, 2215004, 2215616, 2215624, 2215632, 2216949, 2231430, 2231488, 2231678, 2231783, 2231784, 2232570, 2232987, 2236931, 2236932, 2236933, 2239365, 2239366, 2241497, 2243115, 2243828, 2244914, 2245669, 2259583, 2326450	Y
		R03CC02	620955, 620963, 874086, 894249, 894257, 1932691, 2035421, 2063689, 2091186, 2146843, 2146851, 2164434, 2164442, 2165368, 2165376, 2212390, 2213435, 2213443, 2213451, 2261324	Y
	Terbutaline	R03AC03	786616	Y
	Orciprenaline	R03CB03	249920, 3891, 2236783, 2229862, 2152568, 2192675	Y
Long-acting beta-agonists (LABA)	Salmeterol	R03AC12	2211742, 2214261, 2231129, 2136139, 2136147	Y
	Formoterol	R03AC13	2230898, 2237224, 2237225	Y
ICS and LABA in combination (ICS+LABA)	Budesonide, formoterol	R03AK07	2245385, 2245386	Y

	Fluticasone, salmeterol	R03AK06	2240835, 2245126, 2245127, 2240836, 2240837	Y
Leukotriene receptor antagonists (LTRA)	Montelukast	R03DC03	2247997, 2238217, 2243602, 2238216	Y
	Zafirlukast	R03DC01	2236606	Y
	~~Zileuton~~	~~Not available in Canada~~		
Anti-immunoglobulin E monoclonal antibody	Omalizumab	R03DX05	2260565	Y
Inhaled mast cell stabilizers	Cromoglicic acid (cromolyn)	R03BC01	2231431, 2231671, 2046113, 534609, 555649, 261238, 638641, 2049082, 2219468	Y
Theophylline	Choline theophyllinate	R03DA02	346071, 405310, 441724, 441732, 451282, 458708, 458716, 476366, 476390, 476412, 503436, 511692, 536709, 565377, 589942, 589950, 792934	Y
	Theophylline	R03DA04	156701, 261203, 460982, 460990, 461008, 466409, 488070, 532223, 556742, 575151, 599905, 627410, 631698, 631701, 692689, 692697, 692700, 722065, 1926586, 1926594, 1926608, 1926616, 1926640, 1966219, 1966227, 1966235, 1966243, 1966251, 1966278, 1966286, 2014165, 2014181, 2230085, 2230086, 2230087	Y
	Aminophylline	R03DA05	14923, 178497, 497193, 497193, 497207, 582654, 582662, 868450, 2014270, 2014289	Y
Inhaled anticholinergics	Ipratropium bromide	R01AX03	2246084, 2246083, 2163705, 2163713, 2240508, 2240072	N
		R03BB01	2126222, 2243827, 2231494, 731439, 576158, 2247686, 824216, 2026759, 1950681, 2239131, 2216221, 2210479, 2231785, 2236934, 2236935, 2237134, 2237135, 2239627, 2231135, 2231136, 2231245, 2231244, 2097141, 2097176, 2097168	N
	Ipratropium bromide, fenoterol	R03AK03	02148633	N
	Tiotropium bromide	R03BB04	02246793	N
Other beta-agonists	Epinephrine	R03AA01	2017555, 466417, 525103, 1927582	N
	Ephedrine	R03CA02	2237085, 2229698, 2100231, 2100258, 2243148, 2236722, 2229678, 2219743, 2012111, 2229711, 38121, 2242961, 876534, 893323, 893331, 438847, 2242639, 2126419, 2126400	N
	Isoprenaline	R03AB02	2017652	N
	Orciprenaline	R03AB03	1923870, 1928449, 2017660, 254134, 3859	N
Other corticosteroids	Cortisone	H02AB10	280437, 16241, 16446, 16438	N
	Triamcinolone	H02AB08	2194090, 15016, 15024, 2194082	N

	Prednisone	H02AB07	610623, 598194, 550957, 312770, 252417, 210188, 868426, 868434, 868442, 21695, 232378, 607517, 508586, 156876, 271373, 271381	N
	Prednisolone	H02AB06	21679, 2230619, 2152541, 2245532	N
	Methylprednisolone	H02AB04	1934325, 1934333, 1934341, 30759, 30767, 36129, 30988, 2245406, 2245400, 2245408, 2245407, 2241229, 2231893, 2231894, 2231895, 2232750, 2232748, 2063727, 2063697, 2063719, 2063700, 36137, 2230210, 2230211, 30678, 30651, 30643	N
	Betamethasone	H02AB01	2237835, 36366, 2063190, 176834, 28096, 28185	N
	Hydrocortisone	H02AB09	888222, 888230, 888206, 888214, 30910, 30929, 872520, 872539, 878618, 878626, 30635, 30600, 30619, 30627	N
	Dexamathasone	H02AB02	2261081, 2250055, 213624, 16462, 354309, 716715, 874582, 1977547, 664227, 2204274, 2204266, 295094, 285471, 489158, 2239534, 732893, 732885, 2260301, 2237044, 2260298, 2237046, 2237045, 1946897, 1964976, 1964968, 1964070, 2279363, 783900, 751863, 2311267, 2240687, 2240685, 2240684	N
Other xanthines	Theophylline, combination	R03DA54	545090, 476374, 334510, 356123, 792942, 721301, 317225, 828718, 640093, 828726, 828742, 307548	N
Other anti-allergic agents	Levocabastine	R01AC02	2020017	N
	Ketotifen	R06AX17	2221330, 2176084, 2230730, 2218305, 2231680, 2231679, 600784, 577308	N

2. Details of the statistical models

The main model for the analysis is a conditional logistic regression model stratified within each case and its corresponding controls, with adjustment for gender as well as the exact values of all the parameters used for matching. The coefficient estimated from this model for regular use covariates (rICS rLABA rICSLABA) provides the logarithm of the RR of the outcome for regular users versus no users. The CONTRAST statement in used to estimate the RR between regular users. This effectively means changing the reference group within the same regression model.

In order to estimate the RR between regular users and non-regular users (consisting of no users and irregular users combined), the same model was used, only that the covariates for irregular use (*iICS iLABA iICSLABA*) were removed, so that the coefficient for the regular use variables provide the logarithm of the RR for regular users versus non-regular users of the study drugs.

For the analysis of the impact of the regularity of ICS use among regular LABA users, we created a new variable, *nICSq*, the number three-month periods in the 12 months prior to the index date in which at least one ICS prescription is filled. We recoded the regular ICS+LABA use as regular LABA use (*rLABA=1*) with *nICSq=4*.

The coefficient for *rLABA* captures the independent effect of LABA, the *nICSq* capture the independent impact of the regularity of ICS use, and the interaction term *rLABA*nICSq* captures the impact of the regularity of ICS use among LABA users. For those who received ICS in *n* quarters, the *RR* can be estimated as

.

A similar approach was used to study the impact of the regularity of LABA use among regular ICS users. This time, a variable *nLABAq* was defined as the number three-month periods in the 12 months prior to the index date in which at least one LABA prescription is filled, and the above approach was repeated.

3. Regression coefficients for the main analysis

Variable	Estimate (95% CI)	P-value
Regular ICS use	0.716 (0.630 - 0.815)	<0.001
Regular LABA use	1.802 (1.204 - 2.698)	0.004
Regular ICS+LABA use	0.817 (0.685 - 0.974)	0.024
Age at entry*	1.034 (0.983 - 1.088)	0.194
female	N/A (exact matching)	
Number of asthma-related hospitalization *#	8.860 (6.988 - 11.232)	<0.001
Number of asthma-related outpatient services *	1.081 (1.073 - 1.089)	<0.001
Number of oral or injected steroid dispensations*	1.074 (1.048 - 1.101)	<0.001
Number of nebulised or oral beta-adrenergic agonist dispensations*/10	2.125 (2.065 - 2.187)	<0.001
Number of short-acting beta-agonist dispensations*	1.058 (1.039 - 1.077)	<0.001
Total number of asthma-related drugs (except beta agonists and steroids)*	0.971 (0.956 - 0.986)	<0.001
Number of non-asthma related hospitalizations#	1.218 (1.155 - 1.286)	<0.001
Number of non-asthma related outpatient services/10	0.998 (0.997 - 0.998)	0.013
Number of non-asthma related drug dispensations/10	1.001 (1.000 - 1.001)	0.009
Charlson comorbidity index	1.127 (1.071 - 1.185)	<0.001
High income	0.869 (0.804 - 0.940)	<0.001

** Residual effect after matching, RRs are not nominally interpretable*
 # During the first 12 months after entry
% Top five deciles were considered as high income, estimated at the year of the index date

4- Description and results of sensitivity analyses

The first sensitivity analysis was an 'unadjusted' analysis performed by removing all covariates from the conditional logistic model (this analysis was still based on the matched data and therefore controlled for the effect of asthma severity through matching).

In the second analysis, we adjusted for asthma-severity variables in the regression, but did not match cases and controls on such variables. A history of asthma-related hospitalisation can be a confounding factor in that it often affects subsequent treatment decisions and is also a predictor of future hospitalisations; as such, in a sensitivity analysis we removed subjects that had any history of asthma-related hospitalisation during the baseline period.

In the next analysis, instead of matching on any asthma-related admissions in baseline, matching was performed on the number of such admissions in baseline. This analysis results in total balance of asthma-related admissions in the baseline but also results in loss of some cases because of lack of suitable controls.

Further, oral or injectable corticosteroids might act as a substitute for ICS during episodes of asthma exacerbation; this might result in the termination of exposure to ICS at the time the person is at a high risk of experiencing the outcome, causing a reverse-causality bias. To control for this potential bias, in another sensitivity analysis we combined oral, injectable, and inhaled corticosteroids into one category (so the exposure to ICS in this scenario also includes exposure to oral or injectable corticosteroids).

Similarly, while the intensity of exposure to SABA is a widely used surrogate for asthma severity (23,27,30), patients who initiate LABA might be instructed to stop or reduce their SABA intake irrespective of the underlying asthma severity, potentially causing bias due to the confounding factor being affected by the exposure (31). As such, in another sensitivity analysis we removed the variable representing SABA dispensations from matching and the regression model.

In another sensitivity analysis, we removed the adjustment made in the main analysis for the effect of individuals' stockpiling their medications.

Finally, because the risk of asthma-related death and hospitalisations are potentially correlated, death might act as an informative censoring mechanism. To test if censoring due to asthma-related death might have affected the results, we repeated the analysis using the compound outcome of asthma-related death or hospitalisation.

Table A1: Results of the sensitivity analyses (rate ratios)

Scenario	ICS+LABA vs. ICS	ICS+LABA vs. LABA	ICS+LABA vs. no exposure
Main analysis	**1.14 (0.93 - 1.41)**	**0.45 (0.29 - 0.70)**	**0.90 (0.75 - 1.08)**
With matching but without adjustment for asthma severity	1.10 (0.88 - 1.37)	0.51 (0.33 - 0.79)	0.87 (0.72 - 1.05)
Without matching but with adjustment for asthma severity	1.09 (0.85 - 1.41)	0.34 (0.21 - 0.56)	0.81 (0.65 - 1.00)
Removing individuals with asthma-related hospitalisations in the baseline period,	0.98 (0.77 - 1.25)	0.47 (0.30 - 0.75)	0.78 (0.63 - 0.96)

cases=2,913			
Matching on the number of admissions at baseline *(as opposed to any-asthma-related hospitalisation in the main analysis)*, cases=3,286	1.11 (0.88 - 1.39)	0.50 (0.32 - 0.78)	0.85 (0.70 - 1.04)
Exposure to ICS also including oral steroids	1.01 (0.82 - 1.25)	0.45 (0.28 - 0.72)	0.99 (0.81 - 1.21)
Removing SABA as a covariate from the matching & regression	1.03 (0.82 - 1.29)	0.51 (0.33 - 0.78)	0.81 (0.67 - 0.98)
Not adjustment for stockpiling	1.09 (0.87 - 1.38)	0.46 (0.30 - 0.72)	0.86 (0.70 - 1.05),
Outcome defined as asthma-related death or hospitalisation*, cases=3,346 (27 deaths)	1.13 (0.90 - 1.42)	0.50 (0.32 - 0.78)	0.88 (0.73 - 1.07)
*Asthma-related death was defined as a record of death in the vital statistics database with an ICD-10 code of J45 or J46.			

References

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2. Wells KE, Peterson EL, Ahmedani BK, Severson RK, Gleason-Comstock J, Williams LK. The relationship between combination inhaled corticosteroid and long-acting β-agonist use and severe asthma exacerbations in a diverse population. J. Allergy Clin. Immunol. 2012 May;129(5):1274–1279.e2.

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