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Inhaled Corticosteroids and the Risk of Pneumonia in people with Asthma: A case control study.

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Abbreviations

ICS- inhaled corticosteroids

LRTI- lower respiratory tract infection

Background

In clinical trials the use of inhaled corticosteroids is associated with an increased risk of pneumonia in people with chronic obstructive pulmonary disease but whether the same is true for people with asthma is not known.

Methods

Using primary care data from The Health Improvement Network we identified people with asthma and from this cohort we identified cases with pneumonia/ lower respiratory tract infection, and age and sex matched controls. Conditional logistic regression was used to determine the association between the dose and type of inhaled corticosteroid and risk of pneumonia or LRTI.

Results

There was a dose response relationship between strength of dose of inhaled corticosteroid and risk of pneumonia or lower respiratory tract infection (p-trend <0·001), such that after adjusting for confounders people receiving the highest strength of inhaled corticosteroid (≥1000mcg) had a 1.85 (95% CI 1·56 to 2·19) increased risk of pneumonia or lower respiratory infection when compared to people with asthma who did not have a prescription for inhaled corticosteroids within the previous 90 days.

Conclusion

People with asthma receiving inhaled corticosteroids are at an increased risk of pneumonia or lower respiratory infection with people receiving higher doses at greater risk. Pneumonia should be considered as a possible side effect of inhaled corticosteroids and the lowest dose of inhaled corticosteroids possible should be used in the management of asthma.

Background

Inhaled corticosteroids (ICS) are prescribed widely to people with asthma (1) and chronic obstructive pulmonary disease (COPD) (2) to improve symptoms, maximise lung function and reduce exacerbation risk. Recent evidence suggests that ICS may be associated with an increased risk of pneumonia in people with COPD (3-5).

Although asthma is an independent risk factor for invasive pneumococcal disease (6) it is not known whether ICS are independently associated with an increased risk of pneumonia in people with asthma. We set out to examine whether ICS are associated with an increased risk of pneumonia or lower respiratory tract infection (LRTI) in people with asthma by using computerised primary care data and a matched case-control design.

Methods

We extracted data from the Health Improvement Network (THIN: www.thin-uk.com) database. This database contains electronic medical records of 9·1 million patients collected from over 479 general practices in the U.K. We identified a cohort of people with a recorded diagnosis of asthma after 1/4/2004, aged between 18 and 80. We performed a nested case control study in this cohort; cases were defined by first recorded diagnosis of pneumonia or LRTI using previously defined Read codes for pneumonia (7). The date of the diagnosis of pneumonia/LRTI was considered the index date. Six controls per case were matched to cases based on sex, and age at index date (within three years) from the remaining population of people with asthma. Ethics approval to use data from THIN (The Health Improvement Network) was given by the NHS South-East Multi-centre Research Ethics Committee for studies using pre-collected, anonymised data (Ref number 07/H1102/103).

Our main hypothesis was that the risk of pneumonia/LRTI would be associated with the current use of ICS and for this reason we initially identified all prescriptions for ICS up to 90 days before the index date. In the UK the average duration of a prescription can be up to 90 days. We grouped our ICS according to type into beclometasone dipropionate, fluticasone propionate, budesonide and a combined group of ciclesonide and mometasone furoate. The latter two were combined due to low numbers. Where the type of inhaled corticosteroid was changed in the previous 90 days we defined exposure according to the last

prescription. We excluded individuals who were prescribed more than one type of inhaled corticosteroid inhaler on the same day (n=78).

To define the dose of inhaled corticosteroid we used the dose of drug delivered with each inhalation as information on puffs prescribed per day is recorded inconsistently in primary care datasets. To allow for different dose equivalence between drugs budesonide was considered equivalent to beclomethasone and a dose multiplying factor of 2 for fluticasone propionate was used. For each drug type we defined a high and a low dose based on a cut-point of 200 mcg except for fluticasone where we used a cut point of 250 mcg. These cut points represent the step at which a long acting β2 agonist is introduced in the U.K. asthma guidelines (1).

Our *a priori* confounders were smoking status (most recent recording) and co-morbidity as defined by the use of the Charlson Comorbidity Index score (8). Other potential confounders considered were influenza vaccination in the previous year; number of courses of reliever inhalers in the year previous year, both total, and separated by short acting β_2 agonists and long acting β_2 agonists; effect of oral corticosteroids (number of courses in the year prior to the index date), and Townsend socio-economic status score.

We estimated the association between inhaled corticosteroid use and pneumonia/ LRTI by using conditional logistic regression and various different exposures including, in a step wise fashion, type of inhaled corticosteroid, dose of inhaled corticosteroid and then a combination of type of dose of inhaled corticosteroid. We then adjusted our models for *a priori* confounders and included other confounders if they altered the odds ratios for the exposure/outcome association by more than 10%.

We performed a number of sensitivity analyses to determine if the effect was similar in different patient populations and examined whether the effect was similar for diagnosis of pneumonia versus LRTI. We examined the data after excluding those with diagnosis of bronchiectasis and COPD. We also examined the data only in those individuals who had not changed the type of inhaler in the previous 90 days, and included the number of short acting and long acting inhalers in the last year separately in the model. All analyses were completed in Stata 11 (College Station, Texas).

Results

We identified 9059 people with asthma and pneumonia or LRTI and 54189 age and sex matched controls, from a cohort of 359172 people with asthma (Table 1). The mean age of the population was 58·6 years with a range from 18 to 87. People with asthma and pneumonia/LRTI (cases) were more likely to smoke, had a higher Charlson index (i.e. more comorbid illness), and were from a lower social class as compared to controls (Table 1). People with asthma and pneumonia/LRTI were also more likely to have a co-existent diagnosis of COPD, to have received a flu vaccination in the previous year (Table 1), used more reliever inhalers and had more prescriptions for oral steroids in the previous year, when compared to controls (Table 2).

People with asthma and pneumonia/LRTI were more likely to have a prescription for ICS in the last 90 days than their matched controls (Table 2). After adjusting for confounders the odds ratio for this association was 1·2 (95% CI 1·12 to 1·27) (Table 3).

Steroid Type

We examined the risk of pneumonia/LRTI by inhaled corticosteroid type. After adjusting for confounders, budesonide use demonstrated a small increased risk (on the borderline of statistical significance) for pneumonia/LRTI (OR 1·10, 95% 1·00 to 1·21, p=0·057). There was a higher risk of pneumonia/LRTI in individuals receiving fluticasone propionate (OR 1·48 95% CI 1·37 to 1·59, p<0·001). None of the remaining steroid inhalers were associated with evidence of an increased risk (Table 3).

For fluticasone propionate the results were consistent if the 490 individuals who changed their steroid inhaler in the previous 90 days were excluded. The results were also similar when the cases were separated on a diagnosis of LRTI or pneumonia; the odds ratio for fluticasone propionate use and risk of LRTI (n = 4666) was 1·57 (95% CI 1·41 to 1·75); for pneumonia (n=4392) the odds ratio was 1·42 (95% CI 1·27 to 1·58). The results were consistent when individuals with bronchiectasis were excluded, when the number of short acting and long acting reliever inhalers were included separately in the model and also when individuals with COPD were excluded from the analyses.

For budesonide the size of effect tended to be similar through the analyses, however the significance varied. The following sensitivity analyses produced a significant effect; firstly when individuals with COPD were excluded from the study population (OR for budesonide and risk of pneumonia/LRTI 1·17 95% CI 1·04 to 1·32) and when the case population was restricted to those with pneumonia alone (OR for budesonide 1·72 95% CI 1·37 to 2·17).

Steroid Dose

2·9% of the asthmatics with pneumonia/LRTI were prescribed the highest does of inhaled corticosteroid (≥1000mcg), as compared to only 1% in the control population (p<0·001). There was a dose response relationship between strength of ICS and infection risk (p-trend = p<0·001) such that after adjusting for confounders, individuals on the highest dose of inhaled corticosteroid (≥1000mcg) were 1·85 (95% CI 1·56 to 2·19) times more likely to have a pneumonia/LRTI. (Table 3).

These results remained consistent in the various sensitivity analyses and after excluding the 490 cases with a change of inhaler in the previous 90 days (OR for steroid dose ≥1000mcg 1·82 95% CI 1·53 to 2·16, p-trend <0·001). When separating the cases into pneumonia or LRTI the effect was stronger for pneumonia; for the highest dose of inhaled corticosteroid (≥1000mcg) the odds ratio was 2·06 (95% CI 1·61 to 2·65, p-trend p<0·001) for pneumonia (n= 4393) when compared to an odds ratio of 1·72 (95% CI 1·37 to 2·17) for LRTI (n= 4666), (p-trend <0·001).

In addition, the results for the highest level of ICS were similar if individuals with concomitant COPD were excluded; the odds ratio for people with asthma and pneumonia/LRTI receiving ≥1000mcg was 2.05 (95% CI 1·59 to 2·64 p-trend <0·001).

Steroid dose and type combined

There was a significantly increased risk of pneumonia/LRTI in people with asthma with beclometasone and fluticasone at higher dose (>200mcg), but only fluticasone at lower dose (Table 4). The various sensitivity analyses had similar results.

To try and control for asthma severity as a confounder we lastly restricted our analyses to people only receiving ICS; we used people receiving low dose beclometasone as our baseline group. Using this restricted dataset in the adjusted analyses we found the following; individuals prescribed high dose beclometasone group were 23% more likely to have a pneumonia/LRTI episode (OR 1·23 95% CI 1·00 to 1·53). Prescriptions of low and high dose budesonide and low and high dose fluticasone increased the risk of infection with the largest effect found for people prescribed high dose fluticasone with a 78% (OR 1·78 95% CI 1·19 to 1·83) increased risk of having pneumonia/LRTI as compared to those individuals prescribed low dose beclometasone (Table 5).

Discussion

To our knowledge this is the first study to demonstrate a relationship between inhaled corticosteroid use by type and dose and an increased risk of pneumonia or LRTI in asthma. In our study people with asthma and pneumonia or LRTI were more likely to be receiving high dose ICS. These results were consistent for both a diagnosis of LRTI and for pneumonia and were also similar after a number of different sensitivity analyses, including controlling for asthma severity. The results remained consistent when restricted to people under the age of 40 negating any confounding effect of COPD. There was a clear dose response relationship with higher prescribed doses of inhaled corticosteroid being associated with a higher risk of infection. The only ICS associated with an increased risk of LRTI or pneumonia across all analyses was fluticasone proprionate.

A major strength of this study population is its size. Our study is the largest to date with 9059 cases of pneumonia or LRTI identified. The associations described remained consistent after a number of sensitivity analyses including examining the effect in different age populations, and when excluding a recorded diagnosis of COPD.

Using data from primary care records has limitations; we cannot confirm compliance with inhaled corticosteroid use and we cannot assess device type. Furthermore individuals may be using a drug that was prescribed previous to the 90 day index period however this misclassification would bias the results towards the null hypothesis. Our study also suffers from a similar limitation to the studies of pneumonia in

COPD, namely that a diagnosis of pneumonia was not confirmed radiographically, however the diagnosis of pneumonia and lower respiratory infection has been previously shown to be reasonably accurate (7).

Lower lung function (9) is known to be associated with an increased risk of pneumonia with more severe asthma and lower lung function carrying the highest risk, however the increased risk of pneumonia or LRTI remained despite correction for age, smoking status and Charlson index, reducing the effect of these limitations. We also corrected for the number of oral steroids prescribed in the last year, which is associated with both disease severity and decline in lung function (10), and for use of reliever inhalers which is associated with an increased risk of an adverse asthma outcome (11).

As asthma severity is an independent risk factor for pneumonia (6, 12) we attempted to control for asthma severity as a confounder by restricting our analysis. We used low dose beclometasone as our baseline and analysed only those people who received ICS. This did not substantially change the results and the dose response trend remained unaffected, however we acknowledge that it is impossible to fully remove severity as a confounder.

The possibility that ICS may be associated with an increased risk of pneumonia in obstructive lung disease followed the results of the TORCH (Towards a Revolution in COPD Health) study (5) which study examined the potential benefit of fluticasone propionate and salmeterol on mortality in COPD. The study reported a 19% 3 year rate of pneumonia in patients receiving fluticasone at ≥1000mcg/day corresponding to a significant 1·6 fold increase over placebo.

There have few studies in asthma. A meta-analysis from O'Byrne and colleagues assessed the risk of pneumonia in a retrospective analysis of budesonide use in asthma. The primary data set were all double-blind, placebo controlled trials lasting at least 3 months, involving budesonide (26 trials, n= 9067 for budesonide; n=5926 for the comparator) with 62 cases of pneumonia reported as either an adverse, or serious adverse event for budesonide, and 82 for the comparator. In the primary data set the rate of pneumonia adverse events was 0·5% (rate 10/1000 patient years) for budesonide and 1·2% (19·3/1000 patient years) for placebo. The occurrence of pneumonia serious adverse events was 0·15% for budesonide and 0·13% for placebo, resulting in a hazard ratio of 1·29 (95% CI 0·53-3·12), similar to our

odds ratio of 1·10 for budesonide and risk of pneumonia/LRTI. Overall there was no increased risk with higher budesonide doses or any difference between budesonide and fluticasone propionate (9), however pneumonia was not the primary end point in the trials.

Although our data show a possible dose response relationship, with higher doses of ICS being associated with an increased risk of pneumonia or LRTI the biological mechanism explaining the association between risk of infection in asthma and ICS is not clear. There is contradictory evidence on the ability of ICS to influence bacterial numbers. Mouse models (13, 14) and *in vitro* studies of human bronchial epithelial cells (15, 16) have demonstrated that ICS reduce bacterial load or invasion, whereas steroid treatment can reactivate chronic infection by atypical bacteria, *in vitro* and in animal models (17, 18). People with chronic respiratory disease receiving ICS have also been found to have an increased risk of non-tuberculous mycobacterial infection (19, 20) and altered airway microbiota when compared to normal subjects (21). Studying the lung microbiota to delineate whether asthma itself or treatment with ICS alters the lung microbiome may help answer questions of causation.

Conclusion

We have shown that ICS are associated with an increased risk of pneumonia and LRTI in people with asthma. Our results suggest that the dose of ICS prescribed should be kept to the minimum necessary and that the dose should be stepped down if the patient is well controlled. Furthermore prescribers should consider the possibility that infection, rather than underlying asthma, may be driving symptoms before increasing the dose of inhaled corticosteroid. This may be important before prescribers increase the ICS dose to treat recurrent symptoms. A review and meta-analysis of asthma studies involving ICS and an exploration of the effect of ICS on the lung microbiota are now required.

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Table 1. Demographic data for Cases and Controls

	Cases N=9059 N (%)	**Controls** n=54189 N (%)	**Univariate Odds Ratios**
Gender			
Male	3750 (41.4)	22394 (41.3)	
Females	5309 (58.6)	31795 (58.7)	
Age in years (Mean (SD))	58.6 (17.2)	58.6 (17.2)	
Smoking status			
Never	3165 (34.9)	24125 (44.5)	1.00
Ex	3107 (34.3)	15818 (29.2)	1.51 (1.43 to 1.60)
Current	2315 (25.6)	10403 (19.2)	1.70 (1.60 to 1.80)
Unknown	472 (5.2)	3853 (7.1)	0.93 (0.84 to 1.04)
Charlson Index			
0	3414 (37.7)	28389 (52.4)	1.00
1	3694 (40.8)	19157 (35.4)	1.84 (1.75 to 1.94)
2	1256 (13.9)	4697 (8.7)	2.84 (2.63 to 3.08)
3	481 (5.3)	1413 (2.6)	3.77 (3.35 to 4.23)
4	162 (1.8)	423 (0.8)	4.31 (3.57 to 5.21)
>= 5	52 (0.6)	110 (0.2)	5.41 (3.87 to 7.57)
Townsend Score			
1 High	1789 (19.8)	12562 (23.2)	1.00
2	1744 (19.3)	11297 (20.9)	1.08 (1.01 to 1.16)
3	1746 (19.3)	10649 (19.7)	1.15 (1.07 to 1.230
4	1848 (20.4)	9811 (18.1)	1.32 (1.23 to 1.42)
5 Low	1511 (16.7)	6893 (12.7)	1.54 (1.43 to 1.66)
Unknown	421 (4.7)	2977 (5.5)	0.99 (0.89 (1.11)
Influenza Vaccination			
No	3857 (42.6)	26059 (48.1)	1.00
Yes	5202 (56.4)	28130 (51.9)	1.37 (1.30 to 1.44)
COPD			
No	6857 (75.7)	46653 (86.1)	1.00
Yes	2202 (24.3)	7536 (13.9)	2.24 (2.11 to 2.38)

Table 2. Study population medication use for cases and controls

	Cases N=9059 N (%)	**Controls** n=54189 N (%)	**Univariate Odds Ratios**
Reliever use in the last year			
0	2095 (23.1)	21433 (39.6)	1.00
1-2	1357 (15.0)	9790 (18.1)	1.44 (1.34 to 1.55)
3-6	1617 (17.9)	8995 (16.6)	1.95 (1.81 to 2.09)
7-12	1636 (18.1)	7043 (13.0)	2.61 (2.43 to 2.81)
>=13	2354 (26.0)	6928 (12.8)	3.96 (3.69 to 4.24)
Oral steroid courses in the last year			
0	5949 (65.7)	46061 (85.0)	1.00
1	757 (8.4)	2418 (4.5)	2.45 (2.24 to 2.67)
2-3	736 (8.1)	2136 (3.9)	2.76 (2.53 to 3.02)
4-8	738 (8.2)	1800 (3.3)	3.36 (3.07 to 3.68)
>=9	879 (9.7)	1774 (3.3)	4.20 (3.84 to 4.59)
Most recent ICS in the last 90 days			
No steroids	3988 (44.0)	32662 (60.3)	1.00
Beclometasone	1574 (17.4)	9316(17.2)	1.43 (1.34 to 1.53)
Budesonide	791 (8.7)	3682 (6.8)	1.83 (1.68 to 2.00)
Ciclesonide / Mometasone	8 (0.1)	79 (0.2)	0.85 (0.41 to 1.76)
Fluticasone proprionate	2698 (29.8)	8450 (15.6)	2.74 (2.59 to 2.89)
Inhaled corticosteroids dose (mcg) *			
0	3988 (44.2)	32662 (60.3)	1.00
<200	1581 (17.5)	9014 (16.7)	1.49 (1.40 to 1.59)
200-249	802 (8.9)	4019 (7.4)	1.69 (1.56 to 1.84)
250-399	785 (8.7)	3399 (6.3)	1.99 (1.83 to 2.17)
400-499	246 (2.7)	947 (1.8)	2.25 (1.95 to 2.61)
500-999	1370 (15.2)	3555 (6.6)	3.34 (3.10 to 3.59)
≥1000	257 (2.9)	537 (1.0)	4.23 (3.63 to 4.94)

*was not able to determine strength in 82 individuals

Table 3. Association between dose and type of inhaled corticosteroid use and risk of pneumonia or LRTI

	OR	95% CI	Adjusted OR**	95% CI	Adjusted OR***	95% CI
Any ICS use in the last 90 days						
No	1.00				1.00	
Yes	2.00	1.91 to 2.09	1.20	1.12 to 1.27	1.23	1.07 to 1.44
Inhaled corticosteroids use in the last 90 days						
No steroids	1.00		1.00		1.00	
Beclometasone	1.43	1.34 to 1.53	1.05	0.97 to 1.13	1.13	0.95 to 1.34
Budesonide	1.83	1.68 to 2.00	1.10	1.00 to 1.21	1.13	0.87 to 1.47
Ciclesonide/ Mometasone	0.85	0.41 to 1.76	0.54	0.26 to 1.14	-	-
Fluticasone	2.74	2.59 to 2.89	1.48	1.37 to 1.59	1.57	1.28 to 1.92
Inhaled corticosteroids dose (mcg)*						
0	1.00		1.00		1.00	
<200	1.49	1.40 to 1.59	1.06	0.99 to 1.14	1.16	0.98 to 1.38
200-249	1.69	1.56 to 1.84	1.12	1.02 to 1.23	1.00	0.78 to 1.28
250-399	1.99	1.83 to 2.17	1.24	1.13 to 1.37	1.44	1.09 to 1.90
400-499	2.25	1.95 to 2.61	1.16	0.99 to 1.36	1.18	0.67 to 2.06
500-999	3.34	3.10 to 3.59	1.64	1.50 to 1.80	2.01	1.52 to 2.64
>1000	4.23	3.63 to 4.94	1.85	1.56 to 2.19	2.52	1.05 to 6.01

* n=62882

** adjusted for number of relievers in the last year, Charlson index, smoking, social class, use of oral steroids in the last year.

*** n= 11210; restricted to individuals who were less than 40 years old, did not have a diagnosis of COPD or bronchiectasis, did not change their steroid in the previous 90 days and adjusted for number of relievers in the last year, Charlson index, smoking, social class, use of oral steroids in the last year. (Individuals with Ciclesonide/ Mometasone were excluded from the analyses due to small numbers)

Table 4 Analysis combining type of inhaled corticosteroid and dose with risk of pneumonia or LRTI

ICS use in the last 90 days	**Cases** N (%)	**Controls** N (%)	**Odds Ratio**	**Adjusted Odds Ratio ****	**95% CI**	**Adjusted Odds Ratio *****	**95% CI**
No steroids	3988 (44.0)	32662 (60.3)	1.00	1.00		1.00	
Beclometasone low dose ≤ 200mcg	1293 (14.3)	8049 (14.9)	1.36	1.02	0.95 to 1.11	1.12	0.94 to 1.33
Beclometasone high dose > 200mcg	281 (3.1)	1267 (2.3)	1.91	1.23	1.06 to 1.42	1.33	0.76 to 2.32
Budesonide low dose ≤ 200mcg	568 (6.3)	2824 (5.2)	1.71	1.10	0.99 to 1.22	1.12	0.85 to 1.48
Budesonide high dose > 200mcg	223 (2.5)	858 (1.6)	2.25	1.12	0.95 to 1.33	1.29	0.72 to 2.31
Ciclesonide/ Mometasone ≤ 200mcg	6 (0.1)	56 (0.1)	0.89	0.57	0.23 to 1.34		
Ciclesonide/ Mometasone > 200mcg	2 (0.02)	23 (0.04)	0.74	0.49	0.11 to 2.13		
Fluticasone low dose ≤ 250mcg	1071 (11.8)	4358 (8.0)	2.10	1.29	1.18 to 1.41	1.31	1.03 to 1.67
Fluticasone high dose > 250mcg	1627 (18.0)	4092 (7.6)	3.45	1.69	1.55 to 1.84	2.06	1.57 to 2.69

* n=62882

** adjusted for number of relievers in the last year, Charlson index, smoking, social class, use of oral steroids in the last year

*** n= 11210; restricted to individuals who were less than 40 years old, did not have a diagnosis of COPD or bronchiectasis, did not change their steroid in the previous 90 days and adjusted for number of relievers in the last year, Charlson index, smoking, social class, use of oral steroids in the last year. (Individuals with Ciclesonide/ Mometasone were excluded from the analyses due to small numbers)

Table 5 Restricted analysis of association between type and dose of inhaled corticosteroid in individuals who had a prescription for steroids in the last 90 days use and risk of pneumonia or LRTI, with low dose beclometasone as control group

ICS use in the last 90 days	**OR**	**Adjusted OR****	**95% CI**	**Adjusted OR*****	**95% CI**
Beclometasone low dose ≤ 200mcg	1.00	1.00		1.00	
Beclometasone high dose > 200mcg	1.49	1.29	1.10 to 1.53	1.26	0.59 to 2.68
Budesonide low dose ≤ 200mcg	1.31	1.14	1.00 to 1.29	0.98	0.37 to 1.43
Budesonide high dose > 200mcg	1.89	1.32	1.09 to 1.59	1.67	0.76 to 3.71
Ciclesonide/ Mometasone low dose ≤ 200mcg	0.81	0.66	0.25 to 1.73		
Ciclesonide/ Mometasone high dose > 200mcg	0.45	0.41	0.09 to 1.83		
Fluticasone low dose ≤ 250mcg	1.59	1.33	1.19 to 1.83	1.38	1.00 to 1.93
Fluticasone high dose > 250mcg	2.64	1.78	1.19 to 1.48	2.10	1.44 to 3.07

* n=17380

** adjusted for number of relievers in the last year, Charlson index, smoking, social class, use of oral steroids in the last year

*** n=1372; restricted to individuals who were less than 40 years old, did not have a diagnosis of COPD or bronchiectasis, did not change their steroid in the previous 90 days and adjusted for number of relievers in the last year, Charlson index, smoking, social class, use of oral steroids in the last year. (Individuals with Ciclesonide/ Mometasone were excluded from the analyses due to small numbers)