

# PHARMACOEPIDEMIOLOGY

## Pneumonia risk in asthma patients using inhaled corticosteroids: a quasi-cohort study

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### AIM

Studies have linked the use of inhaled corticosteroids (ICSs) to excess pneumonia risk in chronic obstructive pulmonary disease patients. The risk in asthma patients remains unclear. The objective of the present study was to examine the risk of pneumonia with ICSs in asthma patients aged 12–35 years.

### METHODS

We formed a cohort of asthma patients treated from 1990 to 2007 using Quebec health insurance databases. Subjects were considered currently exposed if they had had an ICS dispensed within the 60 days prior to their pneumonia index event or matched person-moment. Secondary analyses investigated the risk of pneumonia according to ICS dose and type. Rate ratios (RRs) and rate differences (RDs) were both estimated through a quasi-cohort approach.

### RESULTS

The cohort included 152 412 subjects, of whom 1928 had a pneumonia event during follow-up. There was an increased risk of pneumonia associated with current use of ICSs [RR 1.83; 95% confidence interval (CI) 1.57, 2.14] or an excess risk of 1.44 cases per 1000 person-years (RD 1.44; 95% CI 1.03, 1.85). There was an excess pneumonia risk with low doses (RR 1.60; 95% CI 1.06, 2.45), moderate doses (RR 1.53; 95% CI 1.12, 2.08) and high doses (RR 1.96; 95% CI 1.64, 2.34) of ICSs, and with budesonide (RR 2.67; 95% CI 2.05, 3.49) and fluticasone (RR 1.93; 95% CI 1.58, 2.36), specifically relative to no use. When accounting for potential protopathic bias, the risk with current use of ICSs was attenuated (RR 1.48; 95% CI 1.22, 1.78).

### CONCLUSION

ICS use in asthma patients appears to be associated with an increased risk of pneumonia and is present for both budesonide and fluticasone.

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Inhaled corticosteroid (ICS) use increases risk of pneumonia in chronic obstructive pulmonary disease patients.
- One type of ICS was found not to increase the risk of pneumonia in asthma patients.

## WHAT THIS STUDY ADDS

- ICS use appears to be associated with an increased risk of pneumonia in asthma patients.
- Higher doses of ICSs are associated with a higher risk of pneumonia.
- Both fluticasone and budesonide appear to be associated with a risk of pneumonia.

## Tables of Links

TARGETS
<b>Nuclear hormone receptors</b> [2]
Glucocorticoid receptor

LIGANDS	
Beclomethasone dipropionate	Fluticasone
Budesonide	Mometasone
Ciclesonide	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

## Introduction

Inhaled corticosteroids (ICSs) are the first-line treatment for patients with persistent asthma. ICSs have been shown to have a good efficacy and safety profile [3]. However, complications have been found to be linked to ICS use, including a reduction in bone density, ocular hypertension, skin bruising, diabetes onset and progression, suppression of growth in children and decreased immunity [4–7]. Furthermore, the Towards a Revolution in COPD Health (TORCH) trial [8], as well as several large observational studies, found an excess pneumonia risk in chronic obstructive pulmonary disease (COPD) patients treated with ICSs [9, 10].

While the increase in the risk of pneumonia in association with ICS use in COPD patients seems clear, the risk in asthma patients remains contentious. In a meta-analysis of randomized controlled trials involving asthma patients using budesonide or budesonide/formoterol, O'Byrne *et al.* [11] found a significant decrease in the hazard ratio (HR) of pneumonia adverse events, and an inconclusive effect on pneumonia severe adverse events. However, Zhang *et al.* [12] found an almost four-fold increase in *Streptococcus pneumoniae* upper respiratory tract colonization in children using ICSs. In a case–control study with 6857 cases of pneumonia or lower respiratory tract infection (LRTI) among subjects with asthma aged 18–80 years, McKeever *et al.* [13] found an increased risk with ICS use, especially at higher doses. As a result of these contradictory findings, we conducted a population-based cohort study of treated patients with asthma to assess whether ICS use is associated with an increased risk of pneumonia, and to evaluate whether the risk varied according to the dose and type of ICS.

## Methods

### Source of data

The source population was identified from the administrative health databases of the Régie de l'assurance maladie du Québec (RAMQ). This database captures the physician visits, procedures, hospitalizations and demographics for the entire population of the province, consisting of more than 7 million people. The provincial pharmacy claims databases are also included in the RAMQ database, consisting of approximately 42% of the entire Quebec population. This is because the public insurance is available only to people over the age of 65, people without access to a private plan, welfare recipients and children of persons covered by the public plan [14, 15]. As a result, the people of highest income may be underrepresented in this database, as they tend to have private plans; nevertheless, the RAMQ still includes a large number of people of average socioeconomic status [16]. Furthermore, the RAMQ databases have previously been used extensively to conduct epidemiological studies of the risk and benefits of ICSs [7, 9, 10, 17–21], and have been proven valid and comprehensive [22–24].

### Study design

The source population for the present study consisted of all subjects with at least one prescription for a respiratory medication between 1 January 1990 and 31 December 2007. These included: any form of  $\beta$ -agonist, theophylline, ipratropium bromide, tiotropium, sodium cromoglycate, nedocromil, ketotifen, leukotriene antagonists or ICSs. The study population of patients with asthma was formed by restricting the cohort to subjects aged 12–35 years at cohort entry, to stand the best chance of eliminating COPD patients,

as there is often overlap in diagnoses between asthma and COPD among older subjects [25]. Subjects with any mention of COPD prior to cohort entry were also excluded. To ensure a new-user cohort, cohort entry was defined as the date of dispensing of the first prescription, with at least 12 months of no prior respiratory medication use. All subjects in the cohort were followed up from cohort entry to first hospitalization for pneumonia, death, end of RAMQ drug coverage or 31 December 2007, whichever came first.

A population-based quasi-cohort approach was used to allow better representation of the underlying cohort used for the nested case-control analysis [26]. All outcome events were selected, along with their exposure classification at the time of the event. The outcome events were defined as a first hospitalization with a diagnosis of pneumonia of any cause identified in the RAMQ hospitalization database [International Classification of Diseases, Ninth Revision (ICD-9) codes 480–487.0 inclusive; ICD 10 codes J10.0, J11.0, J12–J18] during the cohort follow-up. These hospitalizations include any admissions or deaths due to pneumonia, as well as those with primary or secondary diagnoses of pneumonia. The dates of these hospital admissions were defined as the index pneumonia person-moment (all events and exposures are examined for each person on each day). These outcome events were matched to 10 event-free person-days based on age ( $\pm 1$  year), cohort entry ( $\pm 1$  month) and follow-up ( $\pm 1$  month). When fewer than 10 event-free person-days were available, all available index person-moments were used to match to the outcome index person-moment.

All prescriptions for ICSs, alone or in a combination inhaler, dispensed between the cohort entry date and the index person-moment, were identified. Formulations of ICSs were noted to allow classification into subgroups of budesonide, fluticasone and others, consisting of beclomethasone dipropionate, ciclesonide and mometasone. The estimation of equivalent amount of doses was based on the Canadian asthma consensus report, as well as the National Asthma Education Expert Panel report 2 [27, 28]. Accordingly, the equivalent doses for ICSs are beclomethasone 100  $\mu\text{g}$ , budesonide 80  $\mu\text{g}$ , triamcinolone 200  $\mu\text{g}$ , fluticasone 50  $\mu\text{g}$  and flunisolide 200  $\mu\text{g}$ . The converted doses for each subject are classified into categories of high (fluticasone  $\geq 500 \mu\text{g day}^{-1}$ ), moderate (fluticasone 250–499  $\mu\text{g day}^{-1}$ ) and low (fluticasone  $< 250 \mu\text{g day}^{-1}$ ) [27].

### Data analysis

Both crude quasi-rate ratios (RRs) as well as crude and adjusted quasi-rate differences (RDs) of pneumonia associated with ICS use were estimated using methods proposed by Suissa [26]. Adjusted quasi-RRs with 95% confidence interval (CIs) were estimated by conditional logistic regression to account for matching. Covariates adjusted for included age (matched by design), gender, severity of disease and other comorbidity associated with a risk of pneumonia. Severity of disease was assessed independently of ICS use, via the number of other respiratory medications prescribed and the number of hospitalizations related to asthma in the prior year. For oral corticosteroids, only use within the last 3 months was considered as this

would be an indication of severe asthma or recent asthma exacerbation, and would thus be critical to the risk of pneumonia. We also excluded antibiotic prescriptions in the 30 days prior to the index pneumonia event or matched person-moment as it could represent initial therapy for pneumonia. Other conditions correlated to the risk of pneumonia were measured based on prescriptions for conditions of interest which may cause immune system depression or loss of mobility. These included medications prescribed for diabetes (insulin or oral hypoglycaemic agents), cardiovascular diseases (cardiotropic drugs, antihypertensive agents, diuretics or vasodilators), central nervous system conditions (benzodiazepines, major tranquilizers, anticonvulsants or drugs for parkinsonism) and rheumatic diseases (gold salts, methotrexate, azathioprine, hydroxychloroquine or chloroquine). Use of non-steroidal anti-inflammatory drugs, antidepressants and narcotics were also adjusted for.

Subjects were considered current users of ICSs if they had a prescription dispensed within the 60 days prior to the pneumonia index event or matched person-moment, and non-users otherwise. The primary analysis assessed the risk of pneumonia with all ICS use. Secondary analyses assessed differences in risk by formulation and dose of ICS. Exposed users were further classified into users of fluticasone, budesonide or others, and each ICS dose was further classified into high, moderate and low using their fluticasone-equivalent dosage. All analyses were carried out with non-exposed subjects as the reference group.

Sensitivity analyses were undertaken first to explore possible misclassification of the outcome due to misdiagnosis of pneumonia, by including only hospitalizations with a primary diagnosis of pneumonia, or death from pneumonia while in hospital. Secondly, we included an analysis exploring possible protopathic bias [29], a scenario where it may have been possible that a patient was only prescribed a respiratory medication upon early signs or symptoms of pneumonia which may have been misinterpreted as asthma. In the present analysis, we excluded the last 15 days immediately prior to the pneumonia index event or matched person-moment. In other words, a subject was only considered to be exposed to ICSs if their prescription had taken place between 60 and 16 days, inclusive, prior to the pneumonia or matching person-moment. Thirdly, we separated the non-users of ICSs into past- and never users, defined as having a prescription in the 61–365 days prior to the pneumonia index event or matched person-moment and not having a prescription within the year prior to the event or matching person-moment, respectively. To ensure that we were comparing current users of ICSs to non-ICS users who were being actively treated for asthma, we created a comparison group consisting of subjects currently using other respiratory medication in the 60 days prior to the event or matching person-moment. Respiratory medications other than ICSs included any form of  $\beta$ -agonist, theophylline, ipratropium bromide, tiotropium, sodium cromoglycate, nedocromil, ketotifen or leukotriene antagonists. This analysis was also repeated accounting for protopathic bias by not considering the last 15 days of therapy prior to the pneumonia index event or matched person-moment. In a similar vein, in order to ensure that all subjects had actively

treated asthma at cohort entry, we included a sensitivity analysis where cohort members were more strictly defined as having had three respiratory medication prescriptions including ICSs, on at least two occasions, over the span of 1 year. All analyses were conducted using SAS V.9.4 (Cary, NC). We obtained ethics approval for the study from the Research Ethics Committee of the Jewish General Hospital, Montreal, Quebec, Canada.

## Results

A total of 1 410 169 patients dispensed a respiratory medication were identified between 1 January 1990 and 31 December 2007. After excluding patients outside the age range of 12–35 years, prevalent users and those without enough information in the database, the study cohort consisted of 152 412 subjects (Figure 1). This study cohort was followed up for an average of 4.8 years; subjects were, on average, 24.2 years old at cohort entry and 34.9% were male.

A total of 1928 patients with the outcome of pneumonia hospitalization were then identified. These included all diagnosis entries for pneumonia, including primary, secondary, admission and death. The quasi-cohort consisted of 19 275 person-days (10-to-one matching with one patient having only five control person-moments), selected by incidence density random sampling from a total of 267.3 million person-days of follow-up in the full study cohort. Table 1 shows the baseline characteristics of the quasi-cohort by exposure. The non-users of ICSs were slightly older and there were fewer males at cohort entry: 30.8 years old and 29.8% male, as opposed to 30.4 years of age and 31.0% male in users of ICSs. In addition, the ICS users had a higher

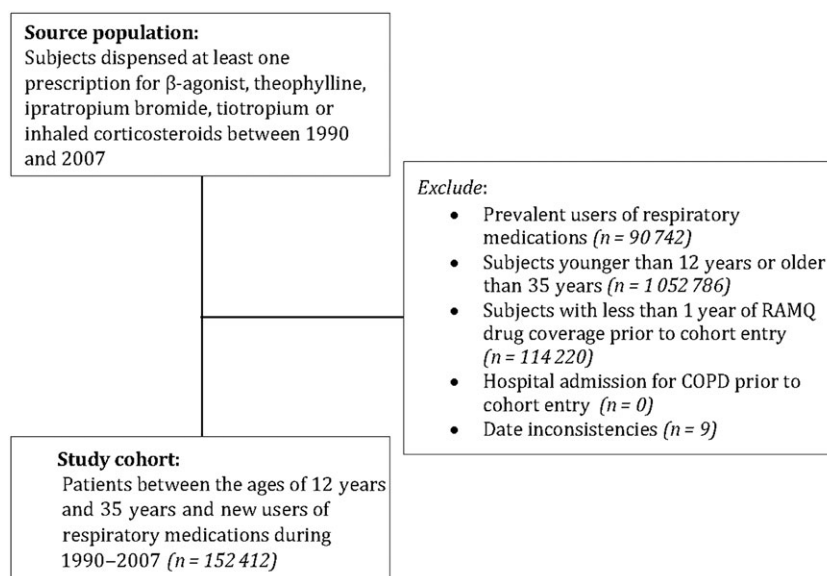
prevalence of markers of asthma severity, and the non-users had a higher prevalence of other comorbidity.

Table 2 shows that, after adjustment for differences in covariates, current ICS use was associated with an 83% increase in the rate of pneumonia hospitalization (RR 1.83; 95% CI 1.57, 2.14), or an excess risk of 1.44 cases per 1000 person-years (RD 1.44; 95% CI 1.03, 1.85). Again, using non-users as the reference group, low-dose ICS was found to be associated with a 60% increase in risk (RR 1.60; 95% CI 1.06, 2.45); moderate dose ICS was associated with a 53% increase in risk (RR 1.53; 95% CI 1.12, 2.08); and high-dose ICS was associated with a 96% increase in risk (RR 1.96; 95% CI 1.64, 2.34). The risk of pneumonia was also found to be increased with use of budesonide by 2.67 times (RR 2.67; 95% CI 2.05, 3.49), and fluticasone by 1.93 times (RR 1.93; 95% CI 1.58, 2.36), while the other ICS group yielded a nonstatistically significant increase (RR 1.23; 95% CI 0.92, 1.63).

## Sensitivity analyses

All results from sensitivity analyses included in the study are shown in Table 3. By excluding subjects with pneumonia as a secondary hospitalization diagnosis, current ICS exposure was found to be associated with a 91% increase in the rate of pneumonia (RR 1.91; 95% CI 1.56, 2.33). Moderate and high doses of ICS were also associated with an excess risk, as well as all types of ICS.

When accounting for potential protopathic bias by excluding the last 15 days of medication use, exposure to ICSs was found to be still associated with a 48% increased risk of pneumonia (RR 1.48; 95% CI 1.22, 1.78), and high doses, budesonide and fluticasone remained associated with an increased, but attenuated risk of pneumonia.



**Figure 1**

Flow diagram describing the assembly of the study cohort using the Régie de l'assurance maladie du Québec (RAMQ) healthcare insurance database. COPD, chronic obstructive pulmonary disease

Table 1

Baseline characteristics of the quasi-cohort based on exposure

Variables	Users	Non-users
<b>Number of subjects</b>	1769, (100.0)	17506, (100.0)
<b>Age (years), mean ± SD</b>	30.37 ± 8.34	30.82 ± 7.89
<b>Sex, n (%) men</b>	549, (31.03)	5213, (29.78)
<b>Hospitalizations in the year prior to index person-moment</b>		
<b>Hospitalization for asthma, n (%)</b>	9, (0.51)	18, (0.10)
<b>Number of hospitalizations for asthma (mean ± SD)</b>	0.01 ± 0.08	0.00 ± 0.03
<b>Hospitalization for pneumonia in the year prior to cohort entry, n (%)</b>	5, (0.28)	30, (0.17)
<b>Respiratory medication use in the year prior to index person-moment</b>		
<b>Respiratory drugs (no. of prescriptions), mean ± SD</b>	3.37 ± 5.89	0.85 ± 2.12
<b>Long-acting muscarinic-receptor antagonists, n (%)<sup>b</sup></b>	2, (0.11)	5, (0.03)
<b>LAMA (no. of prescriptions), mean ± SD</b>	0.01 ± 0.26	0.00 ± 0.13
<b>LABAs, n (%)<sup>b</sup></b>	141, (7.97)	360, (2.06)
<b>LABAs (no. of prescriptions), mean ± SD</b>	0.41 ± 1.88	0.06 ± 0.59
<b>SAMAs, n (%)<sup>b</sup></b>	85, (4.80)	209, (1.19)
<b>SAMAs (no. of prescriptions), mean ± SD</b>	0.26 ± 1.70	0.03 ± 0.48
<b>SABAs, n (%)<sup>b</sup></b>	1287, (72.75)	6352, (36.28)
<b>SABAs (no. of prescriptions), mean ± SD</b>	2.53 ± 3.93	0.68 ± 1.65
<b>Theophylline, n (%)<sup>b</sup></b>	75, (4.24)	916, (5.23)
<b>Theophylline (no. of prescriptions), mean ± SD</b>	0.15 ± 1.31	0.07 ± 0.44
<b>Oral corticosteroids,<sup>a</sup> n (%)<sup>b</sup></b>	173, (9.78)	265, (1.51)
<b>Oral corticosteroids (no. of prescriptions),<sup>a</sup> mean ± SD</b>	0.12 ± 0.48	0.02 ± 0.26
<b>Other medication use in the year prior to index person-moment</b>		
<b>Antibiotics (no. of prescriptions),<sup>c</sup> mean ± SD</b>	1.45 ± 2.08	1.16 ± 1.91
<b>Diabetes drugs, n (%)</b>	72, (4.07)	393, (2.24)
<b>Cardiac drugs, n (%)</b>	204, (11.53)	1523, (8.70)
<b>Central nervous system drugs, n (%)</b>	552, (31.20)	4725, (26.99)
<b>Osteoporosis drugs, n (%)</b>	19, (1.07)	160, (0.91)
<b>Rheumatic Disease drugs, n (%)</b>	4, (0.23)	81, (0.46)
<b>NSAIDs, n (%)</b>	542, (30.64)	4756, (27.17)
<b>Antidepressants, n (%)</b>	367, (20.75)	2622, (14.98)
<b>Narcotics, n (%)</b>	399, (22.56)	3387, (19.35)

LABA, long-acting  $\beta$ -agonists; LAMA, long-acting muscarinic-receptor antagonists; NSAID, nonsteroidal anti-inflammatory drug; SABA, short-acting  $\beta$ -agonists; SAMA, short-acting muscarinic-receptor antagonists; SD, standard deviation

<sup>a</sup>Use in 3 months prior to index person-moment

<sup>b</sup>Not included in analyses

<sup>c</sup>30 days prior to index person-moment is excluded

By further classifying the non-users of ICSs into past and never users, current use was found to be associated with a similar higher risk (RR 1.88; 95% CI 1.60, 2.20), and past use with a nonsignificant risk (RR 1.12; 95% CI 0.96, 1.30).

When only including as non-users of ICSs subjects currently using other respiratory medications, current use of ICSs was found to be associated with a smaller but nevertheless significant increase in risk (RR 1.61; 95% CI 1.38, 1.89). By further excluding the last 15 days prior to the index person-moment, with non-users currently using other respiratory medications as the reference group, the risk of pneumonia remained with current use of ICSs, although the effect was more modest (RR 1.32; 95% CI 1.09, 1.60).

Finally, by limiting the study to subjects with three or more prescriptions for respiratory medications at cohort entry, the results were similar, showing an increase in risk with current use of ICSs, albeit with wider confidence intervals due to the smaller cohort size (578 subjects with a total of 5747 person-days); RR 1.74; 95% CI 1.37, 2.21. Figure 2 summarizes the RR estimates of all sensitivity analyses as compared with the primary analysis using a forest plot.

## Discussion

In a large cohort of over 150 000 patients treated with asthma medications, we found that current ICS use is associated with a significant 83% increase in the risk of being hospitalized for pneumonia. This risk was greatest with higher doses, with the dispensing of 500  $\mu$ g or more of fluticasone-equivalent per day being associated with a 96% increase. This risk remained significant with lower doses of ICSs. This risk was also found to be significant in relation to the use both of budesonide (167% increase in risk) and fluticasone (93% increase in risk). While the risk appears to be greater with budesonide, the confidence intervals overlap, such that we could not conclude that there is a difference in risk between these two agents. With the quasi-cohort approach, we were also able to estimate rate differences, allowing conclusions to be made on the absolute scale. Per 1000 person-years, the overall use of ICSs was found to be associated with 1.44 extra cases of hospitalized pneumonia. When considering the possibility that prescriptions for an ICS near a pneumonia event might actually be due to early signs of pneumonia (protopathic bias), and when restricting the comparison group to subjects with more active treatment for respiratory disease, the risk of pneumonia with current use of ICSs remained but was attenuated at 32% (95% CI of 9%, 60%). The results of these sensitivity analyses addressing confounding by indication as well as protopathic bias are likely to be more representative of the true magnitude of the effect of ICSs on pneumonia risk in asthma patients with similar levels of severity.

Overall, our findings disagreed with the conclusions of the only other study published that directly assessed this relationship; O'Byrne *et al.* [11] found an HR of 0.52 (95%

**Table 2**

Main analysis comparing the risk of pneumonia in ICS users with that in non-users

	No. with pneumonia	No. quasi-cohort (person-days)	Quasi-rates per 1000 person-years	Rate ratio	
				Crude	Adjusted <sup>a</sup> (95% CI)
<b>Total number</b>	1928	19 275	2.63		
<b>Non-users<sup>b</sup></b>	1515	17 442	2.29	1.00	Ref
<b>Current users</b>	413	1833	5.93	2.59	1.83 (1.57, 2.14)
<b>Secondary analysis – dose<sup>c</sup></b>					
<b>Low dose</b>	31	180	4.54	1.98	1.60 (1.06, 2.45)
<b>Moderate dose</b>	72	342	5.54	2.42	1.53 (1.12, 2.08)
<b>High dose</b>	310	1311	6.23	2.72	1.96 (1.64, 2.34)
<b>Secondary analysis – type</b>					
<b>Budesonide</b>	96	362	6.98	3.05	2.67 (2.05, 3.49)
<b>Fluticasone</b>	240	970	6.52	2.85	1.93 (1.58, 2.36)
<b>Other ICSs</b>	77	501	4.05	1.77	1.23 (0.92, 1.63)

CI, confidence interval; ICS, inhaled corticosteroid

<sup>a</sup>Adjusted for all of the factors listed in Table 1 unless otherwise indicated.<sup>b</sup>Reference group (Ref) for primary and secondary analyses; refers to no use of ICS (fluticasone, budesonide, beclomethasone, flunisolide or triamcinolone) in the 60 days prior to the index person-moment.<sup>c</sup>Daily dose in fluticasone equivalents, in  $\mu\text{g day}^{-1}$ ; low (fluticasone  $<250 \mu\text{g day}^{-1}$ ); moderate (fluticasone  $250\text{--}499 \mu\text{g day}^{-1}$ ); high (fluticasone  $\geq 500 \mu\text{g day}^{-1}$ ).

CI 0.36, 0.76) for pneumonia as an adverse event, and 1.29 (95% CI 0.53, 3.12) for pneumonia as a serious adverse event. This discrepancy may be due to the fact that the study by O'Byrne *et al.* obtained outcome data from clinical trials, where pneumonia was recorded as a secondary outcome. This means that these cases are likely to have been milder than those in our study, where our outcome definition was hospitalization for pneumonia. In addition, because patients in clinical trials are more closely monitored, they may be healthier and have better-controlled asthma, putting them at lower risk of being hospitalized for pneumonia. A recent meta-analysis of clinical trials found a lower risk of pneumonia with ICSs, although withdrawals were highly imbalanced between groups [30]. Furthermore, the benefit was no longer significant when excluding the largest trial which included as pneumonia events outcomes such as mucus plugging and atelectasis that may be benefitted by the use of ICSs [30].

However, our findings were comparable with those of other observational studies that have alluded to this relationship [30]. For example, Zhang *et al.*'s [12] cross-sectional study in children found a large and significant increase in the risk of oropharyngeal colonization with *S. pneumoniae* in asthmatic children associated with ICS use, and, while colonization does not necessarily lead to pneumonia, it is likely to increase the risk, especially as *S. pneumoniae* remains a common cause of bacterial pneumonia in children and adults [31]. The case-control study by McKeever *et al.* [13] also found that ICS use is associated with an increase in the risk of pneumonia as well as LRTIs. Furthermore, the latter study found a dose-response relationship in the 18–40-year-old population, where the

results suggested that the risks are higher with higher doses. Similarly, an increased risk in pneumonia associated with ICS use was also found in COPD studies using RAMQ databases [9, 10]. While ICSs are not expected to have the same efficacy and safety profile in COPD patients as in asthma patients, the association between ICSs and pneumonia in COPD patients may be instructive. In these studies, the overall increase in the risk of pneumonia hospitalization was found to be approximately 70%, which is comparable with the risk we found in the present analysis. While COPD patients are more likely to acquire pneumonia as the result of a higher likelihood of lower-airway bacterial colonization [32, 33], the relative risk between ICS users and non-users in COPD and in asthma patients appears to be comparable.

However, the findings of an association between the risk of pneumonia and the different ICSs do not agree with those of previous studies. While previous studies generally found fluticasone to be associated with a higher risk [13, 34], our results showed that budesonide and fluticasone are both similarly associated with a significant increase in the risk of pneumonia. However, in the McKeever *et al.* study [13], only fluticasone was found to be associated with a significant increase in the risk of pneumonia and LRTI in the 18–40-year-old population [13]. In addition, in the COPD case-control study by Suissa *et al.* [10], budesonide was found to be associated with a lower, but still significant 17% increase in risk (95% CI 1.09, 1.26), while fluticasone had a much higher increase in risk (RR 2.01; 95% CI 1.93, 2.10). Other COPD studies included in the Kew *et al.* [34] meta-analysis also showed fluticasone to be associated with an overall higher risk of pneumonia. While the

Table 3

Sensitivity analyses

	No. with pneumonia	No. quasi-cohort (person-days)	Quasi-rates per 1000 person-years	Rate ratio	
				Crude	Adjusted <sup>a</sup> (95% CI)
<b>Sensitivity analysis 1: excluding outcomes of hospitalization with pneumonia as secondary diagnosis</b>					
<b>Non-users<sup>b</sup></b>	933	10 872	1.41	1.00	Ref
<b>Current users</b>	268	1133	3.88	2.76	1.91 (1.56, 2.33)
<b>Sensitivity analysis 2: excluding last 15 days prior to index person-moment</b>					
<b>Non-users<sup>b</sup></b>	1662	18 190	2.41	1.71	Ref
<b>Current users</b>	266	1085	6.46	2.68	1.48 (1.22, 2.78)
<b>Sensitivity analysis 3: classifying non-users into past users and never users</b>					
<b>Never users<sup>c</sup></b>	1201	14 676	2.15	1.00	Ref
<b>Past users</b>	314	2766	2.99	1.39	1.12 (0.96, 1.30)
<b>Current users</b>	413	1833	5.93	2.75	1.88 (1.60, 2.20)
<b>Sensitivity analysis 4: stratifying non-ICS users into current and non-current users of other respiratory medications</b>					
<b>Non-ICS users currently using other respiratory medications</b>					
<b>Current users</b>	413	1833	3.69	1.82	1.61 (1.38, 1.89)
<b>Non-users<sup>b</sup></b>	1257	10 157	2.03	Ref	Ref
<b>Non-ICS users not currently using other respiratory medications</b>					
<b>Current users</b>	413	1833	2.81	6.36	4.81 (3.56, 6.51)
<b>Non-users<sup>b</sup></b>	258	7285	0.44	Ref	Ref
<b>Sensitivity analysis 5: stratifying non-ICS users and excluding last 15 days prior to index-person moment</b>					
<b>Non-ICS users currently using other respiratory medications</b>					
<b>Current users</b>	214	969	3.62	1.67	1.32 (1.09, 1.60)
<b>Non-users<sup>b</sup></b>	1456	11 021	2.16	Ref	Ref
<b>Non-ICS users not currently using other respiratory medications</b>					
<b>Current users</b>	214	969	2.49	6.24	3.07 (2.08, 4.51)
<b>Non-users<sup>b</sup></b>	258	7285	0.40	Ref	Ref
<b>Sensitivity analysis 6: restricting asthma patients to those with three prescriptions on at least two occasions over the span of 1 year</b>					
<b>Current users</b>	189	946	4.58	2.47	1.74 (1.37, 2.21)
<b>Non-users<sup>b</sup></b>	389	4801	1.86	Ref	Ref

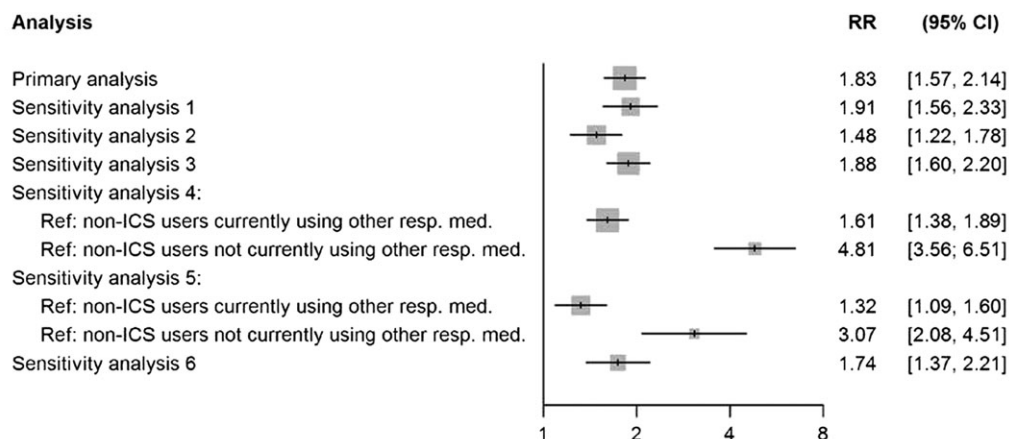
CI, confidence interval

<sup>a</sup>Adjusted for all of the factors listed in Table 1 unless otherwise indicated.<sup>b</sup>Reference group (Ref); refers to no use of ICS (fluticasone, budesonide, beclomethasone, flunisolide or triamcinolone) in the 60 days prior to the index person-moment.<sup>c</sup>Reference group; refers to no use of ICS (fluticasone, budesonide, beclomethasone, flunisolide or triamcinolone) in the 365 days prior to the index person-moment.

pathophysiological differences between asthma and COPD may have contributed to this discrepancy, it is likely that our different outcomes of interest also led to different results. While we included all hospitalizations with pneumonia diagnoses as the outcome of interest, the McKeever *et al.* study [13] also included LRTI as the outcome, and the COPD studies included in the Kew *et al.* meta-analyses [34] were all randomized controlled trials where the cases of pneumonia were principally milder.

The present study had both strengths and limitations. Using the number of prescriptions for all classes of asthma

medications, and asthma hospitalizations present in the year prior to index person-moment, as well as pneumonia hospitalizations and oral corticosteroids use prior to cohort entry, we were able to adjust for both the severity of asthma and other comorbidities, both of which can bias the relationship between ICS use and pneumonia as an outcome. The possibility of residual confounding arising from unmeasured factors remains a concern. For example, in the present study, had the data been available, smoking and other environmental exposures would have been important factors to consider.



**Note:** RRs of current uses of ICS in all analyses performed included in Table 3. Reference groups (Ref.) are also noted in Table 3. Sensitivity analysis 1 excluded all outcomes of hospitalization with pneumonia as the secondary diagnoses. Sensitivity analysis 2 excluded the last 15 days prior to the index person-moment. Sensitivity analysis 3 compared current use of ICS to never use of ICS, defined as not having ICS in the 365 days prior to the index person-moment. Sensitivity analysis 4 further stratified the non-ICS users into those currently using other respiratory medications and those not. Sensitivity analysis 5 not only further stratified the non-ICS users into those currently using other respiratory medications (resp. med.) and those not, it also excluded the last 15 days prior to the index person-moment. Sensitivity analysis 6 restricted subjects to those having had 3 dispensed ICS prescription on at least two occasions over the span of one year.

## Figure 2

Forest plot of rate ratios (RRs) of hospitalization for pneumonia. CI, confidence interval; ICS, inhaled corticosteroid

Similarly, due to the nature of the study, pneumonia outcomes were identified based on diagnosis codes and not confirmed through further clinical testing. It is therefore possible that these cases of pneumonia were in fact episodes of misdiagnosed asthma exacerbation. However, this is unlikely to have explained our results, as previous studies have shown that regular ICS use decreases the risk of asthma exacerbations [35–37]. Furthermore, previous studies have generally shown that the use of database hospital codes in identifying pneumonia outcomes is valid and accurate [38–40]. Patients with asthma in the present study were identified based on only one prescription of respiratory medication. It is likely that some included subjects may not have had asthma, and were only medicated for a temporary condition, would be less likely to receive ICSs and would inherently be at lower risk of pneumonia than patients with true asthma [41]. Such a bias should have been minimized by adjusting for the number of prescriptions for respiratory medications and asthma hospitalizations in the past year. Furthermore, the association persisted after restricting the analysis to patients more likely to have active asthma. Restricting our study to subjects under the age of 35 years will have minimized the inclusion of patients with COPD.

Other strengths of the study stem from our consideration of potential protopathic bias. By excluding the 15 days prior to the index person-moment, we were able to provide results that may better represent the magnitude of the relationship between ICSs and pneumonia in the asthmatic population. In addition, by further classifying the non-users into past and never users, we were able further to understand the duration of the effect that ICSs would have had on the risk of pneumonia.

As was shown in the sensitivity analysis, only current users of ICSs show a significant increase in the risk of pneumonia. Lastly, by using the quasi-cohort approach, we were able not only to represent better the relationship between users and non-users, but also to estimate the risk difference, thus allowing a better representation of the risk on the absolute scale. This can facilitate physicians and decision makers better to understand the magnitude of the impact of the association.

In conclusion, the present study showed that the risk of pneumonia – in particular, serious pneumonia leading to hospitalization – in asthma patients is indeed elevated in relation to ICS use. Both budesonide and fluticasone are associated with a statistically significant increase in the risk of pneumonia. Interestingly, while the conclusions of our study are generally consistent with those of the previous literature, our study further suggests that the risk profile of budesonide is in fact similar to that of fluticasone. However, provided that it is ensured that only patients actively treated for asthma are included, and that the use of ICSs is not in fact a marker for early signs of pneumonia, the increase in risk is relatively small. In future studies, it would be helpful further to validate the diagnosis of pneumonia, identify subjects with a confirmed diagnosis of asthma and adjust for smoking.

## Competing Interests

Dr Samy Suissa has received research grants and participated in advisory board meetings and/or as a speaker at conferences for Boehringer Ingelheim, AstraZeneca, Merck & Co, Novartis and Pfizer.



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