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Risk of pneumonia in asthmatic children using inhaled corticosteroids: a nested case-control study in a birth cohort

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ABSTRACT

Background Inhaled corticosteroids (ICSs) are important in asthma management, but there are concerns regarding associated risk of pneumonia. While studies in asthmatic adults have shown inconsistent results, this risk in asthmatic children is unclear.

Objective Our aim was to determine the association of ICS use with pneumonia risk in asthmatic children.

Methods A nested case-control study was performed in the Mayo Clinic Birth Cohort. Asthmatic children (<18 years) with a physician diagnosis of asthma were identified from electronic medical records of children born at Mayo Clinic from 1997 to 2016 and followed until 31 December 2017. Pneumonia cases defined by Infectious Disease Society of America were 1:1 matched with controls without pneumonia by age, sex and asthma index date. Exposure was defined as ICS prescription at least 90 days prior to pneumonia. Associations of ICS use, type and dose (low, medium and high) with pneumonia risk were analysed using conditional logistic regression.

Results Of the 2108 asthmatic children eligible for the study (70% mild intermittent and 30% persistent asthma), 312 children developed pneumonia during the study period. ICS use overall was not associated with risk of pneumonia (adjusted OR: 0.94, 95% CI: 0.62 to 1.41). Poorly controlled asthma was significantly associated with the risk of pneumonia (OR: 2.03, 95% CI: 1.35 to 3.05; p<0.001). No ICS type or dose was associated with risk of pneumonia.

Conclusion ICS use in asthmatic children was not associated with risk of pneumonia but poorly controlled asthma was. Future asthma studies may need to include pneumonia as a potential outcome of asthma management.

Strengths and limitations of this study

- Our study was a population-based birth cohort study that used longitudinal data and attempted to address major confounders for the study findings such as asthma control status, severity, individual-level socioeconomic status and vaccination status.
- Our study had an epidemiological advantage as our study setting is a self-contained healthcare environment which captures all asthma-related healthcare utilisations.
- Our study had inherent limitations for a retrospective study.
- It was difficult to fully disentangle the effect of asthma control and severity status from inhaled corticosteroid (ICS) use as a confounder because laboratory measures such as spirometry are not available.
- There was lack of confirmation of compliance with ICS use among the patients as we used prescription data.

INTRODUCTION

Asthma is the most common chronic illness affecting 9.6%–13% of children[1 2] and one of the five most burdensome diseases among adults in the USA.[3 4] Approximately 60% of the children with asthma in the USA have persistent asthma[5] requiring use of inhaled corticosteroids (ICSs) as the primary control therapy per National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA) guidelines.[4 6] Moreover, the recently updated GINA 2019 guidelines[7 8] also recommend all patients with asthma to receive either symptom-driven or daily ICS to reduce the risk of asthma exacerbation. Therefore, a large proportion of children with asthma are exposed to ICS.

While ICSs in asthma have shown a good efficacy and safety profile,[6 7] there have been debates regarding the associated risk of pneumonia with long-term use.[9–12] Evidence supporting risk of pneumonia in patients with chronic obstructive lung disease appears to be stronger, however, little is known about the risk of pneumonia associated with ICS use among asthmatic children and previous studies showed inconsistent results.[13–24] Systematic reviews and meta-analysis performed on randomised controlled trials (RCTs) looking at this association have extrapolated the total number of pneumonia

events on the basis of reported adverse events[13 14] rather than looking at pneumonia as a primary end point.

Most observational studies have used International Classification of Diseases (ICD) coding algorithms to identify pneumonia diagnosis among asthmatics, which poses a misclassification bias. Similarly, studies from administrative databases lack asthma-related information such as asthma severity, asthma control status, ICS dosing (as per age group) and other confounders such as vaccination status and socioeconomic status (SES) of the patient.

Better knowledge regarding the safety of ICS, specifically on the association of ICS use with the risk of pneumonia in asthmatic children and potential factors accounting for such association such as asthma severity or control status, will help clinicians and parents' adherence with asthma guidelines as it can reassure clinicians and parents regarding safety concerns.

The aim of our study was to examine the association of ICS use in paediatric patients with asthma of the Mayo Clinic Birth Cohort. Knowledge gained from this study will help to provide an important insight into the nature of impact of ICS on the risk of pneumonia and mitigate the potential impact of parental safety concerns about ICS use on adherence to asthma management recommending ICS use.[25]

METHODS

Study design and setting

This was a nested case-control study from a subset (the Mayo Clinic Birth Cohort) of the Olmsted County Birth Cohort. Olmsted County, southeastern Minnesota, is a virtually self-contained healthcare environment (only two healthcare systems provide clinical care to nearly all Olmsted County, Minnesota residents), and 98% of residents authorise their medical records to be used for research.[26] According to US census data in 2010, the age, sex and ethnic characteristics of Olmsted County residents were similar to those of the state of Minnesota and the Upper Midwest.[27 28] However, Olmsted County has been becoming more diverse as indicated by the racial and ethnic characteristics of children enrolled in public schools (in 2019, 35.2% reported to be non-white).[29] Prevalence of asthma in a population of school-age children Olmsted County, Minnesota, in 2000 (17.6%) was relatively higher than that of children at a national level (12.4%).[30 31]

Study subjects

Patients <18 years of age were identified through an ongoing National Institute of Health (NIH) R01-supported study (HL126667) from a subset of the Olmsted County Birth Cohort (1997–2016) who were born at Mayo Clinic, Rochester, Minnesota, and received their primary care at Mayo Clinic throughout the study period (1997–2017). The details of this cohort have been published previously.[32–34] The exclusion criteria included (1) non-Mayo birth cohort, (2) individuals without research authorisation, (3) insufficient medical records for determining case and exposure status (eg, less than two visits other than delivery during the first 2 years of life), (4) history of chronic diseases making it difficult to discern asthma status (eg, prematurity, bronchopulmonary dysplasia, immunodeficiency, malignancy, pulmonary fibrosis, bronchiectasis, cystic fibrosis, primary ciliary dyskinesia, alpha 1 anti-trypsin deficiency diagnosed by ICD9/ICD10 codes).

Asthma status (both intermittent and persistent asthma) was initially screened using ICD9/ICD10 (493/J45) and confirmed by manual chart review for a physician diagnosis of asthma. Only subjects with confirmed asthma diagnosis by a physician were considered for this study.

Case ascertainment (pneumonia)

All eligible asthmatic children in the birth cohort were initially screened for pneumonia diagnoses 90 days after their physician diagnosis date of asthma through 31 December 2017, using validated ICD9/ICD10 codes (480–487.0/A37, J09.X1 and J10–J18)[35] and confirmed through manual chart review (using Infectious Disease Society of America guidelines).[36 37] There was a 25% false positivity of pneumonia by ICD codes alone. The diagnosis of community-acquired pneumonia requires a patient with a clinically compatible syndrome (fever and cough with or without dyspnoea/sputum production).[36] According to the guidelines, as pneumonia is primarily regarded as a clinical diagnosis (without definitive requirement of chest X-ray for diagnosis and treatment),[37] chest X-ray was not required to be pneumonia cases for this study[38 39] according to guidelines. However, we performed sensitivity analysis among the subset of pneumonia cases with positive chest X-ray repeating unadjusted and adjusted analyses among that subset. For children with multiple episodes of pneumonia, we included only the first episode.

Selection of controls

Controls were selected from the asthmatic subjects who did not develop pneumonia based on the screening described above. Controls were matched 1:1 with cases in term of sex, age and asthma index date (±1 year). Index date for the control was defined by the date of the clinic visit closest to pneumonia event date of the matched case (±1 year). Manual chart review was performed to ensure matched controls did not have diagnosis of pneumonia in the electronic health record (EHR) during the study period.

Exposure status (ICS use)

Exposure was defined as at least 90 days of ICS use prior to index date (eg, a diagnosis date of pneumonia for cases) to have enough duration of exposure to ICS use in relation to the timing of the development of pneumonia. If the ICS was prescribed at least more than 90 days prior to pneumonia, we assumed patient had been on ICS until

pneumonia was developed. This was ascertained using prescription data from EHRs, not claim data. We chose this timeframe for the exposure to ICS by adopting it from other studies, which assessed an association between ICS use and the risk of pneumonia, for fair comparison (online supplemental figure 1).[13]

All prescriptions for ICS, alone or in combination with other inhalers, dispensed between the asthma index date and pneumonia diagnosis were identified and classified into subgroups based on their formulation. Five groups of ICS were identified—(1) beclomethasone metered dose inhaler (MDI), (2) budesonide (dry powder inhaler (DPI) or nebules), (3) ciclesonide MDI, (4) fluticasone (MDI or DPI) and (5) mometasone DPI. Similarly, ICS were grouped into low, medium and high dose depending on total mcg/mg use each day as defined by the NAEPP guidelines (paediatric age-based ICS dose).[6]

Covariates of interest

Other relevant variables were collected from medical record review including: demographic variables (age, gender, race/ethnicity), an individual level HOUsing-based SES measure (HOUSES),[40] pneumococcal vaccination up-to-date status[41] and influenza vaccination status at same year as or prior year to the index date[42] (based on Centers for Disease Control and Prevention guidelines). HOUSES index is a single factor made up of four items (number of bedrooms, number of bathrooms, square footage of the unit and estimated building value of the unit) ascertained from the county assessor's office by matching subjects' addresses which were retrieved from the EHRs with publically available real property data.[40 43] HOUSES index has been validated in numerous studies including asthma and pneumonia-related outcomes.[44 45] Asthma exacerbations (defined as oral corticosteroids use, emergency department (ED) visit or hospitalisation for asthma[6 46]) within 1 year prior to index date were used as a surrogate marker for asthma control status, as most of study subjects did not have information for asthma control status (eg, Asthma Control Test) at the time of pneumonia (no exacerbations vs poorly controlled asthma defined as the presence of at least one asthma exacerbation).[47] The number and frequency of clinic visits was ascertained as a proxy measure of healthcare access to minimise a detection bias (differential identification of mild pneumonia by differential healthcare access). Severity of asthma (intermittent vs persistent) was assessed based on ICS use along with use of other controller medications (long-acting beta adrenergic, leukotriene receptor antagonist, theophylline and so on) according to the NAEPP guidelines.[6]

Patient and public involvement

This was a retrospective, nested case-control study which did not require patient contact, and thus patients were not involved in the design of the study nor subject recruitment. We will follow the NIH research publication policy to disseminate the study results by making the published report available to public freely.

Statistical analysis

Descriptive statistics were used to summarise the characteristics of cases and controls and comparisons were made with Analysis of Variance (ANOVA) for continuous variables, χ^2 for categorical variables and Cochran-Armitage trend test for ordinal variables. Matched analysis via conditional logistic regression accounting for matched pairs was used to determine the association between ICS status as the primary explanatory variable for the risk of pneumonia while controlling for potential confounders identified by univariate analysis. A sensitivity analysis was performed among the subset of pneumonia cases with positive chest X-ray repeating unadjusted and adjusted analyses among that subset. Dosage and type of ICS were additionally reported between the cases and the controls. The literature suggests that the proportion of any ICS use among cases (pneumonia) is 0.5 versus 0.35 in controls.[13] The minimum number of cases (1:1 matching) to obtain 80% of power[48] to detect the difference is 185 subjects. Our study has adequate power to address our primary study aim for the association between ICS use and the risk of pneumonia. All analyses were performed using R statistical software (V.3.6.2; R Core Team, Vienna, Austria).

RESULTS

Study subjects

The characteristics of the subjects are summarised in table 1. We identified 2108 eligible patients with asthma from the birth cohort (n=21 813) of whom 312 children with history of pneumonia during the follow-up period were identified. Forty-one per cent were females and 26% were non-White with the mean age of 2.9 years at asthma diagnosis and 12.7 years at the last follow-up date. Seventy per cent had intermittent asthma and 30% had persistent asthma (23%, 4% and 3% were mild, moderate and severe persistent asthma, respectively).

ICS use and the risk of pneumonia

The results on the associations of ICS use, type and dose with pneumonia are summarised in table 2. ICS use among the cases was 27% whereas ICS use among the matched controls was 22%. Fluticasone was the most commonly used ICS (20.4%) followed by budesonide (2.2 %) among our cohort. Seven subjects were on high dose (1.1%), 19 on medium dose (3%) and 129 on low dose (20.7%) ICS. ICS use was not associated with risk of pneumonia in univariate analysis (OR: 1.30, 95% CI: 0.89–1.88; p=0.16) (table 3 for univariate analysis). After adjusting for pertinent covariates or confounders including number of clinic visits per year, influenza vaccine status and asthma control status, the effect size of ICS use on the risk of pneumonia significantly attenuated in a way resulting in a different direction, although

Table 1 Demographic data for pneumonia case and control subjects

Variables	Cases (n=312)	Controls (n=312)	Total (n=624)	P value
Female, n (%)	128 (41)	128 (41)	256 (41)	1.000*
Race, n (%)				
White	230 (73.7)	231 (74.0)	461 (73.9)	0.153*
Black	35 (11.2)	36 (11.5)	71 (11.4)	
Others	46 (14.7)	38 (12.2)	84 (13.4)	
Unknown	1 (0.3)	7 (2.2)	8 (1.3)	
Age at asthma diagnosis (years), mean (SD)	2.9 (2.4)	2.9 (2.3)	2.9 (2.3)	0.976†
Average number of clinic visits per year, mean (SD)	9.5 (7.3)	7.6 (4.7)	8.5 (6.2)	<0.001†
Influenza vaccine up-to-date status, n (%)	219 (70.2)	202 (64.7)	421 (67.5)	0.146*
Pneumonia vaccine up-to-date status, n (%)	222 (71.2)	221 (70.8)	443 (71.0)	0.930*
HOUSES‡, n (%)				0.828§
Q1 (the lowest)	100 (32.7)	98 (32.2)	198 (32.5)	
Q2	69 (22.5)	78 (25.7)	147 (24.1)	
Q3	63 (20.6)	60 (19.7)	123 (20.2)	
Q4 (the highest)	74 (24.2)	68 (22.4)	142 (23.3)	
Asthma severity, n (%)				0.226§
Intermittent	217 (69.6)	234 (75.0)	451 (72.3)	
Mild persistent	72 (23.1)	57 (18.3)	129 (20.7)	
Moderate persistent	13 (4.2)	16 (5.1)	29 (4.6)	
Severe persistent	10 (3.2)	5 (1.6)	15 (2.4)	
Asthma status, n (%)				<0.001*
Well-controlled	192 (61.5)	238 (76.3)	430 (68.9)	
Poorly controlled	120 (38.5)	74 (23.7)	194 (31.1)	

*Pearson's χ^2 test.
†Linear model ANOVA.
‡HOUSES: an individual-level socioeconomic status measures based on real property data.
§Cochran Armitage trend test.
ANOVA, Analysis of Variance; HOUSES, HOUsing-based socioeconomic status.

statistically not significant (OR: 0.94, 95% CI: 0.62 to 1.41; p=0.75) (table 4 for multivariate analysis).

Other risk factors for pneumonia among children with asthma

Table 2 shows different types or dose of ICS were not associated with the risk of pneumonia (p=0.63 and 0.43, respectively). Both cases and controls were adequately vaccinated with influenza vaccine (70% for cases and 65% for controls) and pneumococcal vaccine (71% each for cases and controls), thus vaccination did not affect risk of pneumonia (p=0.15 and p=0.93, respectively). While association of asthma severity with pneumonia was not found to be statistically significant, poorly controlled asthma status within the past year posed the highest risk of pneumonia, which remained significant after adjusting for other covariates (OR: 2.03, 95% CI: 1.35 to 3.05; p<0.001).

Given the concern about a potential misclassification bias stemming from clinical definition of pneumonia with chest X-ray finding, we performed sensitivity analysis among a subgroup of cases with confirmed pneumonia by positive chest X-ray findings (133/312 (43%)) which did not affect the overall results and interpretation for the association (adjusted OR: 0.87, 95% CI: 0.47 to 1.61; p=0.65) (online supplemental table 1).

DISCUSSION

Our study results showed ICS use was not associated with the risk of pneumonia in asthmatic children in our birth cohort. However, poorly controlled asthma (ie, defined by ICS use, asthma-related ED visits or hospitalisations) was significantly associated with the risk of pneumonia.

Our study finding on the association of poorly controlled asthma with the risk of pneumonia is noteworthy. As a potential mechanism, poorly controlled asthma might cause impairment of innate immunity function and epithelial barrier disruption and which lead to susceptibility to infection such as pneumonia.[49] For example, while impairment of rhinovirus-induced type I and III interferon secretion and its subsequent increased

Table 2 ICS use for pneumonia cases and control subjects

Medication use	Cases (n=312)	Controls (n=312)	Total (n=624)	P value
ICS use, n (%)	85 (27.2)	70 (22.4)	155 (24.8)	0.165*
Type of ICS, n (%)				0.627*
None	227 (72.8)	242 (77.6)	469 (75.2)	
Beclomethasone	5 (1.6)	3 (1.0)	8 (1.3)	
Budesonide	9 (2.9)	5 (1.6)	14 (2.2)	
Fluticasone	67 (21.5)	60 (19.2)	127 (20.4)	
Mometasone	4 (1.3)	2 (0.6)	6 (1.0)	
Dose of ICS, n (%)				0.432†
None	227 (72.8)	242 (77.6)	469 (75.2)	
Low	70 (22.4)	59 (18.9)	129 (20.7)	
Medium	10 (3.2)	9 (2.9)	19 (3.0)	
High	5 (1.6)	2 (0.6)	7 (1.1)	
Non-ICS controller (biologics, cromolyn, LTRA), n (%)	25 (8.0)	21 (6.7)	46 (7.4)	0.540*

*Pearson's χ^2 test.
†Cochran Armitage trend test.
ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonists.

replication of rhinovirus have been widely recognised,[50] such phenomena were not observed in well controlled asthma[51] but those with severe therapy resistant atopic asthma.[52] This might be potentially applicable to bacterial infection. For example, Habibzay *et al* reported that using the intranasal house-dust mite-sensitised mouse model of allergic airway disease, an inflammatory response impaired innate immune function (a reduction in neutrophil recruitment to the airspaces) and led to bacterial invasion and dissemination.[53] Tight junction formation and transepithelial electrical resistance were significantly lower in epithelial cultures from asthmatic donors than from normal controls suggesting that the bronchial epithelial barrier in asthma is compromised.[54]

Given our study results on the associations of poorly controlled asthma status with the risk of pneumonia and the reported under-treatment of asthma with ICS,[55 56] this association does raise an important concern of asthmatic children possibly being suboptimally managed for asthma, resulting in a higher risk of pneumonia. Also, previously claimed ICS use on the risk of pneumonia might have been largely stemming from the inadequately controlled asthma as a major confounder in the literature. Apprehension towards 'stepping-up' the asthma treatment with ICS may deter adequate control of asthma and lead to a worse outcome for patients with poorly controlled asthma. While a short-acting beta2-agonist (SABA) is a historic asthma medication for symptom relief, extensive literature and data suggest that its sole use of SABA is associated with poor long-term asthma control with a higher risk for asthma exacerbation[43 57] and mortality.[58] Moreover, recently updated GINA guidelines have suggested removing SABA monotherapy as a first line of treatment approach among patients with low symptom burden and replacing this with controller medications such as ICS or ICS and formoterol combination as a safer option for better long-term prognosis.[8] Among the cases of our study cohort (312 with pneumonia), 217 (70%) were actually intermittent asthma who had not used ICS or any other controller. With this updated asthma guideline (ie, intermittent use of ICS or ICS combination), risk of pneumonia among intermittent asthma may be reduced through optimal asthma control. More recently, there is an increased understanding that patients considered to have mild asthma have greater morbidity than previously appreciated.[59] This has further necessitated the guidelines to recommend ICSs as a controller treatment option for all patients.[7] This postulation has been further supported in our study by the significant reduction of the effect size of the association between ICS use and the risk of pneumonia after controlling for asthma control status. Despite a relatively small sample size in our study, given the sufficient statistical power to detect the reported effect size for the association between ICS use and the risk of pneumonia, our study results are unlikely to be subject to type II error. Regardless of statistical power or sample size, if ICS use had been associated with the risk of pneumonia, one would expect higher ICS dose to have higher risk of pneumonia, which was not observed in our study. Future asthma studies should consider including pneumonia as a potential outcome of asthma control status as the current outcomes of asthma studies largely focus on asthma control, risk of exacerbation and lung function.[46]

Our study results are consistent with the findings reported by Cazeiro *et al* based on a meta-analysis for children with asthma.[19] The meta-analysis of nine trials that revealed at least one event of pneumonia showed a reduced risk of pneumonia in patients taking ICS (risk ratio (RR): 0.65, 95% CI: 0.44 to 0.94). However, the meta-analysis including all 31 trials revealed no significant

Table 3 Univariate analysis for the association between factors and risk of pneumonia

Variables	OR	95% CI	P value
ICS use			
No	1	reference	
Yes	1.30	0.89 to 1.88	0.163
HOUSES*			
Q1 (the lowest)	1	reference	
Q2	0.88	0.56 to 1.37	0.569
Q3	1.02	0.66 to 1.57	0.938
Q4 (the highest)	1.09	0.71 to 1.69	0.690
Average number of clinic visits per year	1.09	1.04 to 1.14	<0.001
Influenza vaccine up-to-date status			
No	1	reference	
Yes	1.29	0.92 to 1.82	0.142
Pneumonia vaccine up-to-date status			
No	1	reference	
Yes	1.05	0.57 to 1.94	0.876
Asthma severity			
Intermittent	1	reference	
Mild persistent	1.39	0.92 to 2.09	0.121
Moderate persistent	0.87	0.39 to 1.94	0.737
Severe persistent	2.01	0.68 to 5.92	0.205
Asthma status			
Well-controlled	1	reference	
Poorly controlled	2.28	1.54 to 3.37	<0.001

*HOUSES: an individual-level socioeconomic status measures based on real property data.
ICS, inhaled corticosteroid.

difference in the risk of pneumonia between the ICS and placebo groups (risk difference: −0.1%; 95% CI: −0.3% to 0.2%). Also, O'Byrne *et al* reported no significantly increased risk of pneumonia with ICS use (HR=1.29, 95% CI: 0.53 to 3.12) based on a 3-month double-blind, placebo-controlled trial.[16] Although pneumonia was not the primary outcome in the study (reported as an adverse outcome) and results were based on pooling multiple randomised controlled studies in a subgroup analysis, they found no significant difference in the incidence of pneumonia between fluticasone-treated versus budesonide-treated groups. Moreover, a protective effect of ICS on the risk of pneumonia (not requiring hospitalisation) was observed in the study (occurrence of pneumonia was 0.5% for budesonide and 1.2% for placebo).[16] Similarly, a recent clinical trial which tested high-dose ICS (quadrupling dose: >1000 µg/day vs low ≤1000 µg/day of beclomethasone) showed no association of high-dose ICS use with the risk of pneumonia.[15] An earlier RCT showed the safety of ICS on the risk of infection by comparing ICS treatment versus placebo. The results, indeed, showed a significant decrease from before to after therapy in the percentage of days of upper respiratory tract infection (21% to 10% ICS vs 19% to 16% placebo) and lower respiratory tract infection (LRTI) (30% to 15% ICS vs 27% to 21% placebo).[60]

On the other hand, some studies have shown the opposite effect.[13 14 61 62] In a nested case-control study found an increased risk of pneumonia and LRTI with only fluticasone use (OR: 1.58, 95% CI: 1.29 to 1.93) in adult patients with asthma.[13] The study used administrative codes (ICD9 codes) for case ascertainment, however, did not account for asthma control status, vaccination status and frequency of clinic visits. A retrospective study by Qian *et al* using Quebec health insurance database found an increased risk of pneumonia associated with current ICS use (RR 1.83, 95% CI: 1.57 to 2.14) with incremental dose relation (RR 1.60 for low dose, RR 1.53 for medium dose and RR 2.67 for high dose ICSs).[14] The study again did not clearly define and adjust for major confounders such as asthma control or severity status and others such as vaccination history and SES. Moreover, the study only took account of hospitalised cases of pneumonia. In summary of the literature, prospective studies based on RCT or meta-analysis on the association between ICS use and the risk of pneumonia do not support such association while retrospective studies based on administrative data claim such association raising study design issues as described above given the inherent limitations of retrospective studies based on administrative claims data. These retrospective studies could get an analytic benefit from application of a validated asthma control index using claim data in paediatric population which might potentially account for the association between ICS use and the risk of pneumonia.[63]

Table 4 Association between use of ICS and risk of pneumonia from a multivariate conditional logistic regression model*

Variables	Adj. OR	95% CI	P value
ICS use, yes versus no	0.94	0.62 to 1.41	0.75
Average number of clinic visits per year	1.07	1.02 to 1.12	0.003
Influenza vaccine up-to-date status, yes versus no	1.08	0.75 to 1.56	0.68
Asthma status, poorly controlled versus well-controlled	2.03	1.35 to 3.05	<0.001

*Model included, any ICS Use, average number of clinic visits per year, influenza vaccine up-to-date status and asthma control status.
Adj. OR, adjusted OR; ICS, inhaled corticosteroid.

Our study is a community-based birth cohort study that used rigorous approaches for ascertaining ICS use and pneumonia incidence through longitudinal data with definite follow-up period of paediatric patients at Mayo Clinic, Rochester, Minnesota, USA. This is a first paediatric population-based birth cohort study demonstrating ICS use not to be associated with risk of pneumonia in asthmatic children. The study has also attempted to control for major confounders like asthma control status, severity, individual-level SES and vaccination status (pneumonia and influenza) which are inadequately addressed by previous retrospective studies.

Our study has inherent limitations as a retrospective study. While our case ascertainment for pneumonia was consistent with current guidelines,[38 64] we did not include chest X-ray finding in pneumonia case ascertainment which might result in a misclassification bias. To address this concern, we performed sensitivity analysis among a subgroup of cases with confirmed pneumonia by positive chest X-ray findings (133/312 (43%)) which did not affect the overall results and interpretation for the association (adjusted OR: 0.87, 95% CI: 0.47 to 1.61; p=0.65) (see online supplemental table 1). As discussed above, it is difficult to fully disentangle the effect of asthma control and severity status from ICS use as a confounder as retrospective studies did not have precise and accurate measure of asthma control and severity status around the time of pneumonia (eg, Asthma Control Test score, lung function measures and so on). Also, we were not able to quantify and take into account the exposure to ICS or systemic steroid (eg, total ICS or systemic steroid dose during the follow-up period) as pharmacy claim data were not available to our study. Also, the proportion of patients not on ICS was higher in our cohort, which may have caused decreased exposure to ICS. Another limitation in our study lies in the lack of confirmation of compliance with ICS use among the patients as we used prescription data. While this is a limitation of our study as a retrospective study, accurate measurement of compliance in even prospective studies is often challenging as claim or self-report may not necessarily be accurate. As with a retrospective study using medical index search codes (eg, ICD codes), the major limitation remains on the accuracy of the ICD codes used for asthma and pneumonia diagnosis. To address this concern, we did perform a manual chart review to verify the accuracy of the coded cases of pneumonia and excluded incorrectly coded diagnoses. It is noteworthy that we found misclassification of pneumonia (false positive rate of 25%) by manual chart review which may pose an important implication on interpretation of retrospective studies based on claim data.

In conclusion, ICS use in asthmatic children was not associated with risk of pneumonia but poorly controlled asthma was. Future asthma studies may need to include pneumonia as a potential outcome of asthma control status. Our findings will need to be verified in larger, prospective cohort studies.

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Contributors PS conceptualised and designed the study, designed the data collection instrument, collected and interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript. C-IW designed the study, collected and interpreted the data, reviewed and revised the manuscript. KSK designed the data collection instruments, carried out the analyses, and reviewed and revised the manuscript. ER conceptualised and designed the study, designed the data collection instrument, supervised data analyses, and reviewed and revised the manuscript. JHK designed the data collection instrument, reviewed and revised the manuscript. SS, HL, MP conceptualised and designed the study, reviewed and revised the manuscript. YJ (guarantor) conceptualised and designed the study, supervised data collection and analysis, interpreted the data, and reviewed and finalised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability statement Data are available upon reasonable request. The datasets generated and/or analysed during the current study are not publicly available as they include protected health information. Access to data could be discussed per the institutional policy after IRBs at Mayo Clinic approves it.

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