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Original Article

Treatment of allergic rhinitis reduces acute asthma exacerbation risk among asthmatic children aged 2–18 years

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Abstract *Background/purpose:* Asthma and allergic rhinitis (AR) frequently coexist in the same individuals in childhood and adolescence. We evaluated whether AR had an impact on acute exacerbation (AE) and whether intranasal corticosteroid (INCS) and second-generation antihistamines (SGH) for AR modified the association of AR with AE in asthmatics aged 2–6 years and 7–18 years.
Methods: Using the National Health Research Institutes (NHRI) Database 2005 of Taiwan, we investigated patients who had been diagnosed with asthma in the years 2000 through 2012 and who had then been followed-up with for at least one year. The risk factors of AE were evaluated using multiple Cox proportional hazards regression analysis.
Results: The incidence of AE was higher in the preschool group than the older group (adj. HR: 1.68, 95% CI: 1.44–1.95). The AR with INCS and/or SGH group was found to have a lower risk of AE than the non-AR group (adj. HR: 0.32, 0.44 and 0.30), but the AR without treatment group did not have a significant difference with the non-AR group. After propensity score matching, the use of INCS and/or SGH was associated with a significant reduction in the occurrence of AE among AR patients aged 2–6 years old (adj. HR: 0.38, 0.57 and 0.45) and 7–18 years old (adj. HR: 0.50, 0.52 and 0.35).
Conclusion: The preschool patients had a higher incidence of AE than the older patients in general. Adequate treatment with INCS and/or SGH in asthma with AR patients is important for reducing the incidence of AE of asthma.

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Introduction

The prevalence of childhood asthma and allergic rhinitis (AR) in Taiwan has been increasing.[1] Asthma and AR are the two most common chronic disorders and frequently coexist in the same individuals in childhood and adolescence.[2] Recent data has shown a very high rate of comorbidity between asthma and rhinitis, as approximately 60—80% of children with asthma have symptoms of AR.[3,4]

AR may aggravate asthma management and lead to poor asthma control and outcomes.[3] A previous study reported that asthmatic patients who had AR exhibited a significantly higher risk of asthma attacks and emergency visits in adulthood.[5] Furthermore, a meta-analysis study found that the use of intranasal corticosteroid (INCS) significantly improved some asthma-specific outcome measures in children and adults having both AR and asthma,[6] while another study reported that treatment with INCS in AR and asthma patients was associated with a reduced risk for subsequent asthma-related ED (emergency department) visits.[7]

Three different patterns of recurrent wheeze in children have been proposed the concepts of transient early wheezing in the first 3 years, non-atopic wheezing in the preschool years and IgE-mediated persistent asthma.[8] However, age is one of the determinants of asthma phenotype in childhood. If symptoms are well-controlled between episodes and usually follow a cold, then viral-induced asthma is the most appropriate diagnosis. The virus-induced asthma phenotype seems to be the most common among preschoolers.[9] Over time, such virus-induced asthma appears to decline substantially, typically disappearing completely by 6 years of age. IgE-associated wheeze/asthma are more common in school age and adolescents.[10]

The National Health Insurance (NHI) program of Taiwan provides health care and coverage to the vast majority of the nation's population, with 91% of medical institutions being under NHI contract. The National Health Insurance Research Database (NHIRD) is a comprehensive database of the ambulatory care and inpatient care claims data of the patients served by the NHI program, making it one of the world's most extensive health care databases and one that has, accordingly, yielded invaluable data for a range of epidemiological studies.[11,12] As noted above, different age groups typically experience differing prevalence rates of different asthma phenotypes; therefore, the aims of this study were to determine the prevalence rates of AR among asthmatic children and to assess whether different age groups of asthmatic children with or without AR have an increased incidence of acute exacerbation (AE) of asthma using data from the NHIRD. In addition, this study investigated whether treatment of AR with INCS reduced the risk of AE in asthmatic children of different ages.

Methods

Data resources

The data subjected to analysis in the present study were taken retrospectively from a subset of the NHIRD called the Longitudinal Health Insurance Database 2005 (LHID2005) that is managed by Taiwan's National Health Research Institutes (NHRI). The NHI program began operating in 1995, and currently covers 99.5% of the residents of Taiwan. The data included in the LHID2005 consists of the claims data for 1 million patients randomly selected from the 2005 registry for the NHIRD, which in turn contains all the claims data collected from January 1, 1997, to December 31, 2013. This study selected data from 2000 to 2012 to ensure that every patient's medical history could be traced for at least a three-year period. This database, which is made available upon approved application to scholars conducting various forms of academic research, provides a scrambled patient ID number, date of birth, gender, diagnostic codes (which follow the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes), and prescription drug information, among other pieces of basic data, for each of the patients included within it. This study was approved by the Ethics Committee of Chia-Yi Christian Hospital in Taiwan (Institutional Review Board No. CYCH-IRB: 106092)

Study population

The current study was a population-based cohort study that sought to determine the relationship between AR and asthma with AE among asthma patients. Specifically, the study investigated patients who had been diagnosed with asthma, meaning those who had been diagnosed with asthma (ICD-9-CM: 493.X) more than 3 times within any 90-day period from the years 2000 through 2012, who had used an asthma controller, and who had then been followed-up with for one year. The term "asthma controller" was used to refer to cases in which the asthma patient had to use one of the following at least one time during the period from the first diagnosis date of asthma to AE or the date one year from the diagnosis date: inhaled corticosteroid (ICS), combination inhaled corticosteroid and long-acting beta-agonists (ICS plus LABA), or leukotriene receptor antagonists (LTRAs). ICS include beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, and mometasone, any of which can be delivered in a preparation designed to be inhaled. LABA include formoterol and salmeterol, while LTRAs include montelukast and zafirlukast. However, any patients with incomplete insurance claims data or who were younger than 2 years of age or older than 18 years of

age were excluded. We divided the patients meeting the inclusion criteria into two groups based on age; one group consisted of preschool children (those aged 2—6 years old), and the other group consisted older, school-age children (those aged 7—18 years old).

Outcome

The primary outcome of interest in the present study was the occurrence of AE of asthma. Furthermore, in order to ensure that only cases of AE were included as the primary outcome, any asthma patients (ICD-9-CM: 493.X) treated with short-acting beta2-adrenergic agonists or anticholinergic agents, such as terbutaline, albuterol sulfate, or ipratropium inhalation solution, were included, with the outcome of "AE" in this study meaning both diagnosis and treatment with one of those medications on the same day. The period of observation during which this outcome was checked for was the year following the date of the initial diagnosis of asthma. For a given patient, the endpoint was either the date on which the patient visited an ED or was hospitalized for acute asthma or the date one year from the first diagnosis date of asthma.

Allergic rhinitis

AR (ICD-9-CM: 477.X) is among the conditions that commonly co-occur with asthma. In this study, a given patient had to have a diagnosis of AR recorded at least 3 times within one year in the database's diagnosis field prior to his or her endpoint date and had to have used AR medication, including an INCS and/or second-generation antihistamine (SGH), in order to be designated as having AR. AR with INCS and/or SGH medication means that the AR patient had to use INCS and/or SGH at least one time during the period from the first diagnosis date of asthma to AE or within one year from the first diagnosis date of asthma. The different types of INCS included Avamys, Flixonase, Nasacort, Pulmicort and Nasonex nasal spray, and the different types of SGH included Cetirizine, Levocetirizine, Loratadine, Deslortadine and Fexofenadine.

Comorbidities

The three most frequently contributing comorbid conditions reported in asthmatic patients are rhinitis, sinusitis, and gastroesophageal reflux disease (GERD).[13] The baseline comorbidities, including acute sinusitis (ICD-9-CM: 461.X) and GERD (ICD-9-CM: 530.81), were determined for each patient between the date of the asthma diagnosis to AE or one year from the first diagnosis date.

Statistical analyses

With respect to categorical variables, the data were expressed in terms of frequencies (percentages), whereas for continuous variables, the data were expressed as means $\pm$ standard deviations (SDs). The Student's t-test was utilized to compare the AE and non-AE groups with respect to parametric continuous data, whereas the categorical data of the two groups were compared using the Chi-square test. The risk factors of AE, meanwhile, were evaluated using multivariate Cox proportional hazards regression analysis with adjustments for potential risk factors (age, gender, asthma drug, acute sinusitis, and GERD). We also identified 634 patients with AR who did not receive any treatment during the period from the first diagnosis date of asthma to the end date, and used 1:4 propensity score matching to select 4795 counterpart controls who received treatment.

All the statistical analyses were conducted using SPSS for Windows, Version 21.0 (IBM Corp., Released 2012. Armonk, NY, USA), and a two-tailed p value of <0.05 was regarded as indicative of statistical significance.

Results

Demographic characteristics

In this study cohort, the prevalence of AE among asthma patients within a year was investigated. The basic demographic characteristics of the asthmatic patients in the two groups are listed in Table 1. Out of the total cohort of 10,708 asthma patients, 850 patients (7.94%) received emergency treatment or were hospitalized with AE within one year of the date of the initial asthma diagnosis (Table 1). The number of asthma patients was greater among the patients aged 2—6 years old (N = 6506) than among the patients aged 7—18 years old (N = 4202). 5429 patients (50.7%) had AR in the total cohort of 10,708 asthma patients. The rate of AR was 54.71% in the patients aged 2—6 years old (N = 2970) and was 45.29% in the patients aged 7—18 (N = 2459).

A higher risk of AE in the patients aged 2—6 years old

Table 2 shows the risk factors of AE among all the asthma patients, as well as the specific risk factors for the patients aged 2—6 and 7—18, respectively. The prevalence of AE was higher in the preschool (2—6 years old) group than the older (7—18 years old) group (adj. HR: 1.68, 95% CI: 1.44—1.95). The prevalence of AE did not differ significantly between male and female patients.

A lower risk of AE in the asthma with AR patients using INCS and/or SGH than in the non-AR patients, but not in the asthma with AR patients not using INCS and/or SGH than in the non-AR patients regardless of age group

To determine whether a diagnosis of AR recorded at least 3 times within one year in the database's diagnosis field prior to the endpoint date had an impact on AE in the asthma patients, we set the endpoint for a given asthma patient as either the date on which the patient visited an ED or was hospitalized for acute asthma or the date 1 year from the first diagnosis date. To determine whether the use of INCS or SGH to treat AR modified the association of AR with acute AE, we assumed that the use of INCS and/or SGH at least one time during the period from the first diagnosis date of

Table 1 Demographic characteristics in asthma patients with different status of acute exacerbation.

	overall	Non-AR[a]	AR[a]	*p* value
	N = 10,708	N = 5279	N = 5429	
Age, Mean (SD)	6.25 (3.36)	5.87 (3.34)	6.63 (3.33)	<0.001
2–6 years old	6506 (60.76)	3536 (66.98)	2970 (54.71)	<0.001
7–18 years old	4202 (39.24)	1743 (33.02)	2459 (45.29)	
Gender				
Female, N (%)	4435 (41.42)	2248 (42.58)	2187 (40.28)	0.016
Male, N (%)	6273 (58.58)	3031 (57.42)	3242 (59.72)	
Asthma Drug				
ICS[b], N (%)	3125 (29.18)	1537 (29.12)	1588 (29.25)	<0.001
LTRAs[c], N (%)	1077 (10.06)	2476 (46.90)	2203 (40.58)	
ICS + LABA[d], N (%), N (%)	4679 (43.70)	489 (9.26)	588 (10.83)	
ICS + LTRAs, N (%)	794 (7.41)	372 (7.05)	422 (7.77)	
ICS + LABA + LTRAs, N (%)	1033 (9.65)	405 (7.67)	628 (11.57)	
Comorbidity				
Acute sinusitis, N (%)	6348 (59.28)	2907 (55.07)	3441 (63.38)	<0.001
GERD[e], N (%)	12 (0.11)	3 (0.06)	9 (0.17)	0.092
AR Drug				
AR without treatment	634 (5.92)	–	634 (11.68)	–
AR with INCS[f], N (%)	2151 (20.09)	–	2151 (39.62)	
AR with SGH[g], N (%)	1294 (12.08)	–	1294 (23.83)	
AR with INCS and SGH, N (%)	1350 (12.61)	–	1350 (24.87)	
AE[h]	850 (7.94)	601 (11.38)	249 (4.59)	<0.001

[a] AR: Allergic rhinitis.
[b] ICS: Inhaled corticosteroid.
[c] LTRAs: Leukotriene receptor antagonists.
[d] LABA: Long-acting beta-agonists.
[e] GERD: Gastroesophageal reflux disease.
[f] INCS: Intranasal corticosteroids.
[g] SGH: secondary generation antihistamine.
[h] AE: Acute exacerbation.

asthma to AE indicated AR with INCS, AR with SGH, or AR with INCS and SGH. The AR without treatment group did not have a significant difference with the non-AR group (HR: 0.78, 95% CI: 0.59–1.02), but the AR with INCS and/or SGH group was found to have a lower risk of AE within one year of follow-up than the non-AR group (HR: 033, 95% CI: 0.27–0.42; 0.39, 95% CI: 0.30–0.51; 0.28, 95% CI: 0.21–0.38). The risk of AE in the AR with treatment groups was also found to be lower than that in the non-AR group after adjustments were made for age, gender, asthma controller, acute sinusitis, and GERD (adj. HR: 032, 95% CI: 0.26–0.41; 0.44, 95% CI: 0.34–0.58; 0.30, 95% CI: 0.22–0.40) (Table 2). The same results were also found in the different age groups (Table 3). These results indicated a lower risk of AE in the AR patients with INCS and/or SGH treatment, but no reduced risk in the AR patients without treatment compared to the non-AR patients.

LTRAs lowered the risk of AE among the asthma patients aged 2–6 years old, but not among the patients aged 7–18 years old

To determine whether the use of asthma controllers to treat asthma modified the association with AE, we assumed that the use of an asthma controller, for example, ICS, ICS plus LABA, or/and LTRAs, at least one time during the period from the first diagnosis date of asthma to AE indicated asthma with controller usage. LTRAs lowered the risk of AE among patients with asthma compared to the use of ICS (adj. HR: 0.58, 95% CI: 0.49–0.70) (Table 2), but the risk of AE was not reduced by the use of ICS plus LABA in the asthma patients (adj. HR: 1.18, 95% CI: 0.94–1.49), while the use of ICS plus LTRAs or ICS plus LABA plus LTRAs increased the risk (adj. HR: 1.62, 95% CI: 1.29–2.03; 1.90, 95% CI: 1.54–2.34). A negative relationship between AE and the use of LTRAs was found in the patients aged 2–6 years old (Adj. OR: 0.52, 95% CI: 0.42–0.65), although no such relationship was found among the patients aged 7–18 years old (Adj. OR: 0.74, 95% CI: 0.54–1.03) (Table 3). These results indicated a lower risk of AE in the asthma group treated with LTRAs for the patients aged 2–6 years old but not for the patients aged 7–18 years old compared to the asthma group treated with ICS. The above results also indicated that the combination of two or three controllers resulted in a higher risk of AE than treatment with ICS.

Use of INCS and/or SGH reduced the risk of AE compared to no use of INCS and/or SGH in the AR patients

Table 4 shows the risk factors of AE among all of the 5429 asthma patients with AR. 4795 asthma patients with AR had

Table 2 Risk factor of acute exacerbation in patients with asthma.

	Crude HR (95%CI)	[#] Adj. HR (95%CI)
Age		
7—18	Ref.	Ref.
2—6	1.30 (1.12,1.49)***	1.68 (1.44,1.95)***
Gender		
Female	Ref.	Ref.
Male	1.09 (0.95,1.25)	1.10 (0.96,1.26)
Asthma Drug		
ICS[a]	Ref.	Ref.
LTRAs[b]	0.62 (0.52,0.74)***	0.58 (0.49,0.70)***
ICS + LABA[c]	1.13 (0.89,1.42)	1.18 (0.94,1.49)
ICS + LTRAs	1.62 (1.29,2.03)***	1.62 (1.29,2.03)***
ICS + LABA + LTRAs	1.66 (1.35,2.04)***	1.90 (1.54,2.34)***
AR [d]		
Non-AR	Ref.	
AR	0.39 (0.33,0.45)***	
AR Drug		
Non-AR	Ref.	Ref.
AR without treatment	0.78 (0.59,1.02)	0.89 (0.68,1.17)
AR with INCS[e]	0.33 (0.27,0.42)***	0.32 (0.26,0.41)***
AR with SGH[f]	0.39 (0.30,0.51)***	0.44 (0.34,0.58)***
AR with INCS and SGH	0.28 (0.21,0.38)***	0.30 (0.22,0.40)***

[a] ICS: Inhaled corticosteroid.
[b] LABA: Long-acting beta-agonists.
[c] LTRAs: Leukotriene receptor antagonists.
[d] AR: Allergic rhinitis.
[e] INCS: Intranasal corticosteroids.
[f] SGH: secondary generation antihistamine.
[#] Adjusted for gender, acute sinusitis, asthma drug, gastroesophageal reflux disease.
*: <0.05; **: <0.01; ***: <0.001.

been prescribed INCS and/or SGH at least one time during the period from the first diagnosis date of asthma to AE. The use of INCS and/or SGH was associated with a significant reduction in the occurrence of AE compared to no use of INCS and/or SGH among the patients aged 2—6 years old (adj. HR: 034, 95% CI: 0.21—0.55; 0.45, 95% CI: 0.28—0.72; 0.36, 95% CI: 0.22—0.60) and the patients aged 7—18 years old (adj. HR: 047, 95% CI: 0.28—0.79; 0.49, 95% CI: 0.28—0.87; 0.26, 95% CI: 0.13—0.50). Similar results were also found in the propensity score matching analysis of the patients aged 2—6 years old (adj. HR: 038, 95% CI: 0.22—0.66; 0.57, 95% CI: 0.32—1.03; 0.45, 95% CI: 0.34—0.85) and the patients aged 7—18 years old (adj. HR: 050, 95% CI: 0.29—0.88; 0.52, 95% CI: 0.28—0.99; 0.35, 95% CI: 0.17—0.72) (Table 4). The above data support the conclusion that regardless of the patient's age, the use of INCS and/or SGH is associated with a reduced risk of the occurrence of AE among patients with AR.

Discussion

In this study, we found that the patients aged 2—6 years old had a higher incidence of AE than the patients aged 7—18 years old. The asthma with AR patients who used INCS and/or SGH had a lower risk of AE compared to the asthma without AR patients, but the same was not true of the asthma with AR patients who received no treatment. LTRAs reduced the risk of AE among the asthma patients aged 2—6 years old but not among the patients aged 7—18 years old. Meanwhile, the patients treated with a combination of two or three controllers had a higher risk of AE than those treated with ICS. Our results also demonstrated that the use of INCS and/or SGH in AR patients could reduce the risk of AE in comparison to no treatment in the AR patients regardless of age group.

A previous report revealed that the rates of asthma-related ED visits and hospitalization were highest among preschool children in the United States.[14] Our study found that the patients aged 2—6 years old had a higher incidence of AE than the patients aged 7—18 years old. The classifications of various wheezing phenotypes have been proposed according to either the different triggers of wheezing (with such classifications including "episodic viral wheeze", which is triggered only by colds, and "multiple-trigger wheeze", which is also triggered by other factors),[15] or the time course (with such classifications including "early transient", "persistent", and "late-onset" wheeze)[9] among preschool children. Optimal strategies for preventing asthma with AE are important due to the high prevalence rate of asthma with AE in preschool children. However, appropriate methods of preventing asthma with AE are not well defined in recurrent wheezing by age 6 years. A meta-analysis study supported the use of daily ICS to prevent exacerbations in

Table 3 Risk factor of acute exacerbation in each age groups with asthma.

	Crude HR (95%CI)	# Adj. HR (95%CI)
Age 2—6		
Asthma Drug		
ICS[a]	Ref.	Ref.
LTRAs[b]	0.56 (0.45,0.69)***	0.52 (0.42,0.65)***
ICS + LABA[c]	1.03 (0.74,1.44)	1.06 (0.76,1.47)
ICS + LTRAs	1.48 (1.13,1.94)**	1.51 (1.15,1.98)**
ICS + LABA + LTRAs	1.81 (1.41,2.33)***	1.96 (1.53,2.53)***
AR [d]		
Non-AR	Ref.	Ref.
AR without treatment	0.90 (0.62,1.30)	1.05 (0.72,1.52)
AR with INCS[e]	0.35 (0.26,0.46)***	0.31 (0.23,0.42)***
AR with SGH[f]	0.42 (0.30,0.59)***	0.48 (0.34,0.66)***
AR with INCS and SGH2	0.37 (0.26,0.52)***	0.38 (0.26,0.54)***
Age 7—18		
Asthma Drug		
ICS[a]	Ref.	Ref.
LTRAs[b]	0.69 (0.50,0.95)*	0.74 (0.54,1.03)
ICS + LABA[c]	1.35 (0.97,1.89)	1.34 (0.96,1.87)
ICS + LTRAs	1.71 (1.12,2.61)*	1.84 (1.21,2.82)**
ICS + LABA + LTRAs	1.43 (1.00,2.06)*	1.76 (1.23,2.53)**
AR [d]		
Non-AR	Ref.	Ref.
AR without treatment	0.70 (0.47,1.05)	0.74 (0.49,1.10)
AR with INCS[e]	0.32 (0.23,0.47)***	0.33 (0.23,0.48)***
AR with SGH[f]	0.35 (0.22,0.54)***	0.37 (0.24,0.59)***
AR with INCS and SGH	0.18 (0.11,0.32)***	0.19 (0.11,0.34)***

[a] ICS: Inhaled corticosteroid.
[b] LABA: Long-acting beta-agonists.
[c] LTRAs: Leukotriene receptor antagonists.
[d] AR: Allergic rhinitis.
[e] INCS: Intranasal corticosteroids.
[f] SGH: secondary generation antihistamine.
[#] Adjusted for gender, acute sinusitis, asthma drug, gastroesophageal reflux disease.
*: <0.05; **: <0.01; ***: <0.001.

preschool children with persistent asthma and the use of high-dose intermittent ICS to prevent exacerbations in preschool children with intermittent asthma or viral-triggered wheezing.[16] A previous study of 2- to 5-year-old children with intermittent asthma showed that once-daily montelukast significantly reduces asthma exacerbations compared with placebo.[17] Maintenance treatment with inhaled corticosteroids or montelukast is recommended for the treatment of wheezing disorders in preschool children.

In the present study, LTRAs were found to reduce the risk of AE among the asthma patients aged 2—6 years old, but not the asthma patients aged 7—18 years old. The majority of preschool children with recurrent wheezing have intermittent exacerbations triggered by viral upper respiratory tract infections,[9] whereas the relative incidence of atopic AE is smaller.[18,19] Preschool children with recurrent wheezing should be classified into the episodic viral wheeze phenotype, which has been shown to respond better to LTRAs than ICS.[20] One previous study demonstrated elevated cysteinyl leukotrienes and leukotriene B4 in the nasopharyngeal secretions and urine of children with viral induced wheeze and found that emergency department visits were reduced by 45% by montelukast.[21] In addition, adherence to LTRAs is better than adherence to ICSs.[22,23] We recommend LTRAs as the first-line therapy for children aged 2—6 years with frequent intermittent or mild persistent asthma. Stepwise treatment escalation based on disease severity or symptom control level is a global strategy for asthma management.[24] More severe or uncontrolled asthma requires the use of more asthma controller. More severe or uncontrolled asthma also increases the risk of AE.[25] Our study demonstrated that treatment with a combination of two or three controllers resulted in a higher risk of AE than treatment with ICS. We suggest that more severe or uncontrolled asthma may increase the risk of AE.

Past studies have reported that concomitant AR in patients with asthma resulted in poor asthma control and more emergency room visits compared with asthma patients without concomitant AR.[3,5,26] However, our study showed that the prevalence of AE was significantly lower among the AR patients with treatment, regardless of whether that treatment consisted of INCS or SGH, than among the non-AR patients within the overall cohort of asthma patients, including those aged 2—6 years old and

Table 4 Risk of acute exacerbation in asthma patients with allergic rhinitis.

	Total		PS matching
	Crude HR (95%CI)	[#] Adj. HR (95%CI)	[#] Adj. HR (95%CI)
Age 2—6			
Asthma Drug			
ICS[a]	Ref.	Ref.	Ref.
LTRAs[b]	1.00 (0.65,1.53)	0.87 (0.55,1.36)	0.66 (0.38,1.17)
ICS + LABA[c]	1.85 (1.04,3.27)*	1.73 (0.97,3.08)	1.60 (0.79,3.26)
ICS + LTRAs	1.45 (0.80,2.63)	1.45 (0.79,2.65)	0.84 (0.34,2.09)
ICS + LABA + LTRAs	2.28 (1.38,3.76)**	2.41 (1.44,4.03)***	1.60 (0.78,3.30)
AR [d]			
AR without treatment	Ref.	Ref.	Ref.
AR with INCS[e]	0.38 (0.24,0.60)***	0.34 (0.21,0.55)***	0.38 (0.22,0.66)***
AR with SGH[f]	0.47 (0.29,0.75)**	0.45 (0.28,0.72)**	0.57 (0.32,1.03)
AR with INCS and SGH	0.41 (0.25,0.66)***	0.36 (0.22,0.60)***	0.45 (0.34,0.85)*
Age 7—18			
Asthma Drug			
ICS[a]	Ref.	Ref.	Ref.
LTRAs[b]	1.23 (0.70,2.17)	1.16 (0.65,2.07)	1.43 (0.75,2.75)
ICS + LABA[c]	2.13 (1.15,3.93)*	1.88 (1.01,3.51)*	2.25 (1.12,4.52)*
ICS + LTRAs	1.42 (0.57,3.53)	1.39 (0.56,3.44)	1.67 (0.61,4.61)
ICS + LABA + LTRAs	2.41 (1.32,4.41)**	2.57 (1.40,4.71)**	1.93 (0.90,4.14)
AR[d] Drug			
AR without treatment	Ref.	Ref.	Ref.
AR with INCS[e]	0.46 (0.28,0.76)**	0.47 (0.28,0.79)**	0.50 (0.29,0.88)*
AR with SGH[f]	0.49 (0.28,0.86)*	0.49 (0.28,0.87)*	0.52 (0.28,0.99)*
AR with INCS and SGH	0.26 (0.14,0.51)***	0.26 (0.13,0.50)***	0.35 (0.17,0.72)**

[a] ICS: Inhaled corticosteroid.
[b] LABA: Long-acting beta-agonists.
[c] LTRAs: Leukotriene receptor antagonists.
[d] AR: Allergic rhinitis.
[e] INCS: Intranasal corticosteroids.
[f] SGH: secondary generation antihistamine.
[#] Adjusted for gender, acute sinusitis, asthma drug, gastroesophageal reflux disease.
*: <0.05; **: <0.01; ***: <0.001.

those aged 7—18 years old (Tables 2 and 3). One previous study found that AR was associated with more severe asthmatic symptoms, poorly controlled asthma, and exacerbations, but not with low lung function.[27] In that study, participants with AR had higher lung function as measured by peak flow and higher FEV1 than those without AR. Another study also reported that the median percentage predicted FEV1 was significantly higher in participants with AR.[28] One study of adult asthmatics revealed that patients with lower FEV1 values were at significantly higher risk for asthma AE.[29] Another study of child asthmatics also found that lower FEV1/FVC ratios are associated with severe exacerbation.[30] In addition, greater airway hyperresponsiveness was associated with a greater decline in FEV1 after exercise challenge.[31] Reduced FEV1 has been shown, meanwhile, to be an important risk factor for asthma AE. Based on these earlier studies, it is possible that the higher lung function and FEV1 seen in AR may be one factor affecting the risk of asthma exacerbation. We suggest that AR increases pulmonary function and FEV1 and may not cause an increase of the AE of asthma.

While AR is known to be among the most commonly occurring chronic diseases of childhood, the appropriate diagnosis is not made for a majority of symptomatic children. One study reported that 76.2% children had symptoms of AR but that only 56.1% of these children had been diagnosed with the condition by a physician.[3] Another study found that 77.7% of pediatric bronchial asthma patients also had symptoms of AR.[32] As such, the impacts of AR on both individual patients and their families, as well as on society in general, are frequently underestimated.[33] In this study, only 50.7% of the asthma patients had a concomitant diagnosis of AR. Our study further showed that the prevalence of AE was significantly lower among the AR patients with treatment. As such, we should take care not to miss a diagnosis of AR in an affected asthma patient, because by applying an appropriate treatment for AR, the proper control of asthma to avoid AE is more likely.

A meta-analysis study found that INCS significantly decreased rescue medication use in children and adults having both AR and asthma.[6] A nested, case—control study further found that INCS and/or SGH treatment of concomitant AR was associated with reductions in the risk of emergency room treatment and hospitalization for asthma in patients with asthma.[34] Our study revealed that the use of INCS and/or SGH in patients having both AR and asthma

could reduce the risk of AE in those aged 7—18 years old and in those aged 2—6 years old compared to the risk in asthma patients with AR receiving no treatment. We thus suggest that INCS and/or SGH treatment of concomitant AR is effective in asthmatic children.

The strengths of the study included a large, real-world sample of patients and nationwide prescription data. Most of the previous studies of the relationship between childhood AR and asthma have focused on distribution data alone or have consisted of randomized clinical trials. However, there were limitations to this association study. For example, the validation of AR and asthma may be problematic, because the study population was extracted from the NHIRD based on arbitrary coding by physicians, while the NHIRD lacks laboratory data confirming the correct diagnosis of AR and asthma. In clinical settings, asthma treatment decisions are based on the level of asthma control in the previous weeks or months, but it is not easy to check the level of asthma control with the data contained in the NHIRD. Misclassification bias could also have been an issue in this study since not all instances of AE occurred in ERs or resulted in hospitalization. For example, the probability of emergency treatment or hospitalization for mild AE is reduced by the use of bronchodilators in OPDs, with such lack of emergency treatment or hospitalization making it undetectable according to our definition. Additionally, the study data may have been affected by possible residual confounding, such as cases of respiratory viral infection increasing the rate of AE.

In conclusion, our findings indicated that the preschool-aged children had a higher incidence of AE than the older children. LTRAs reduced the risk of AE among the asthma patients aged 2—6 years old group. Patients aged 2—6 years old group. Optimal treatment strategies with LTRAs are the first-line therapy for preventing asthma with AE in preschool children. The occurrence of AE among the asthma with AR patients in this study was significantly reduced by the use of INCS and/or SGH. Adequate treatment with INCS and/or SGH is thus more likely to improve asthma control in AR patients. The incidence of AR is frequently underestimated. As such, the appropriate diagnosis of AR is important so that AR can be properly controlled to reduce the worsening of asthma. Appropriate diagnosis of AR in asthma patients and adequate treatment with INCS and/or SGH in asthma with AR patients are important for reducing the AE of asthma.

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