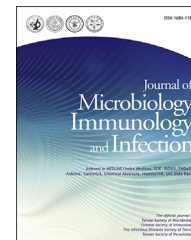




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Original Article

# Allergic rhinitis as a key factor for the development of gastroesophageal reflux disease in children



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Received 24 December 2019; received in revised form 18 July 2020; accepted 7 August 2020  
Available online 18 August 2020

## KEYWORDS

Allergic rhinitis (AR);  
Asthma;  
Gastroesophageal  
reflux disease  
(GERD);  
Children

**Abstract** *Background:* Gastroesophageal reflux disease (GERD) may cause airway symptoms and some airway diseases exacerbate GERD symptoms. Asthma and allergic rhinitis (AR) have been identified as united airway disease because of their similar epidemiology and pathophysiology. Asthma has been considered a risk factor to develop GERD. However, the association between AR and GERD is not clear. We tried to investigate whether AR could increase the development of GERD.

*Methods:* Children diagnosed as AR without a prior history of GERD were conducted from the National Health Insurance Research Database between 2000 and 2005. After propensity score matching, we enrolled 36,588 children with AR and 36,588 non-AR children as the controls. Cox regression models were adopted to calculate the hazard ratio (HR) of GERD.

*Results:* AR children had a significantly increased risk of GERD than non-AR children (adjusted HR 1.91, 95% CI = 1.73–2.11,  $p < 0.001$ ), especially in the age less than 6 years old (adjusted HR 2.68, 95% CI = 1.64–4.38,  $p < 0.001$ ). The risk factor related to increased risk of GERD including age, gender, and chronic sinusitis.

*Conclusion:* AR is a risk factor associated with the development of GERD in children.

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## Introduction

Gastroesophageal reflux (GER) is a common physiological or pathological process with the intermittent ascent of gastric acid contents into the esophagus. GER disease (GERD) is present when reflux of gastric contents causes symptoms or complications.<sup>1</sup> GERD affects approximately 10% of western populations and reported to be significantly associated with atopic diseases, specifically asthma.<sup>2,3</sup> GERD is a complex problem in children and several suspected respiratory manifestations of GERD, such as asthma, chronic cough, and laryngitis, are commonly encountered in the pediatric group.<sup>4</sup> Patients with GERD are more likely to have atopic conditions and asthma when compared with patients without GERD.<sup>4</sup>

Asthma is a common and chronic airway disease that the main pathophysiological features are bronchial obstruction and airway inflammation. The possible relationships between GER and respiratory symptoms of asthma are complex. Asthma may lead to GER, and GER may exacerbate asthma or cause asthma-like symptoms.<sup>2,5</sup> Furthermore, GERD with gastrointestinal symptoms is also more common in asthmatics as against controls. Clinical or endoscopic evidence of GERD is also in a significantly higher proportion of the asthmatics as compared to the controls.<sup>6</sup> Despite the high prevalence of GERD in asthma, a causal link is still lacking. One of the potential explanations of this link is the comorbid GERD. GERD is significantly more occurrence in asthmatics as compared to the controls.

The pathogenesis of atopic disorders is known to involve a complex interplay of genetic and environmental factors. There is strong evidence in a relationship between AR and asthma in children.<sup>7,8</sup> AR was an independent risk factor for

asthma in the primary care study population and patient with physician-diagnosed AR increased the risk almost fivefold for a future asthma diagnosis.<sup>9</sup> Treatment of allergic rhinitis (AR) would reduce acute asthma exacerbation risk among asthmatic children aged 2–18 years.<sup>10</sup> A positive association between asthma development and preceding 5-year antibiotic exposure in AR children has been reported.<sup>11</sup> Asthma and rhinitis are common allergic and respiratory diseases with a marked predominance in children and the increasing prevalence of atopic disorders has been documented.<sup>12–14</sup> The AR and asthma are the phenotypes of airway diseases with Th2-driven prominent nasal allergic inflammation with a high specific age or a positive response to allergen provocation test.<sup>15</sup> However, the effect of AR on newly-onset GERD is still unknown and the underlying factors linking AR and GERD remain to be elucidated. In the present study, we would like to explore the relationship between AR and the development of GERD in different age groups of children.

## Methods

### Data source

The study database was using claims data from National Health Insurance Research Database (NHIRD), which is managed by the Taiwan National Health Research Institute (NHRI). The National Health Insurance (NHI) program reimburses the health care costs of 99% of the population in Taiwan. The NHIRD contains comprehensive healthcare information for all of Taiwan's insured individual, including demographic data, clinical visited date, diagnostic codes,

and prescription details. For this study, we tapped a subset of NHIRD known as the Longitudinal Health Insurance Database (LHID) 2005. This study uses a subset of NHIRD known as the Longitudinal Health Insurance Database (LHID) 2005. This dataset contains ambulatory and inpatient care medical record for one million randomly sampled population enrolled into the NHI system in the year 2005. According to the NHRI, there are no statistically significant differences in age, gender, or healthcare costs between the LHID 2005 and NHIRD. The diseases diagnosed were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

### Statement of ethics

The study protocol was approved by the Institutional Review Boards of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20150168). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the relevant regulations. The informed consent in this study was waived because the data obtained from a national research database which cannot identify any subject's identity. This study involved no more than minimal risk to the subjects and the study could not practically be carried out without the waiver.

### Study population

We defined the patient having GERD or AR if the patient had at least 2 times of corresponding ICD-9-CM code in the diagnosis field. The patients between January 1, 2000, and December 31, 2005, with AR (ICD-9 code: 477.8, 477.9) at least 2 times were defined for the AR cohort. The non-AR control children, who had never diagnosed as AR, were matched to AR cohort by age, gender and selected comorbid medical disorders by propensity score and were 1:1 randomly selected. The date of first diagnosed AR for each patient was defined as the index date. Subjects were excluded if they were more than 18 years old, had GERD diagnosed before the index date, or had incomplete follow-up insurance data.

### Diagnosis of GERD

The outcome of interest was a diagnosis of ICD-9-CM 530.81 (gastroesophageal reflux disease, GERD). The American academy of pediatrics guideline for the management of gastroesophageal reflux in children,<sup>16</sup> medication is not used in every child with GERD. Therefore, we did not consider the use of disease-related medications to strengthen the diagnosis of GERD. Patients were followed from the index date to the new onset of GERD, death, disenrollment from the national health insurance, or the end of the study date (December 31, 2013), whichever came first.

### Potential confounders

It has been reported that the children with AR also had atopic dermatitis in 30.3%.<sup>17</sup> AR, chronic rhinitis, acute or chronic sinusitis have shared symptoms but are different diseases with

different etiologies.<sup>18</sup> Therefore, atopic dermatitis (ICD-9 code: 691.8), chronic rhinitis (ICD-9 code: 472.0), sinusitis (ICD-9 code: 461, 473), and nasal polyps (ICD-9 code: 471) were considered as comorbidities in the present study. Inpatient and outpatient files from the year prior to the index date were used to obtain information on co-morbidities.

### Statistics analysis

Pearson chi-square test or Fisher's exact test was evaluated differences in categorical variables between AR cohort and non-AR cohort. Independent T-test was evaluated differences of two cohorts in continuous variables. Cox proportional-hazards regression analysis was performed to examine the risk of GERD in the AR cohort compared with the non-AR cohort during the follow-up period. Several co-variables, including age, gender, co-morbidities, were adopted in the statistical analysis model. Hazard ratios (HR) and 95% confidence intervals (CI), using non-AR cohort without asthma history as the reference, were calculated to show the risk of GERD in the interaction analysis between AR and asthma. A Kaplan–Meier curve was used to estimate the probability of GERD, and the log-rank test was used to evaluate the differences between with AR cohort and non-AR cohort. All statistical operations were performed using the SAS 9.3 statistical package; all p-values were 2-sided, and p-values < 0.05 were considered significant.

## Results

### Demographic data for the study subjects

A total 36,588 children with AR and 36,588 children without AR during Jan 1, 2000, to Dec 31, 2005, were included in this study after 1:1 propensity score matching. Patient demographic characteristics between the AR cohort and non-AR cohort at baseline are present in Table 1. The mean age of the AR cohort and the non-AR cohort were  $10.3 \pm 4.9$  and  $10.3 \pm 4.9$  years old, respectively. The distribution of

**Table 1** Demographic characteristics between the non-AR cohort and the AR cohort.

|                                      | Non-AR group<br>(n = 36588) |        | AR group<br>(n = 36588) |        | p value |
|--------------------------------------|-----------------------------|--------|-------------------------|--------|---------|
|                                      | n                           | (%)    | n                       | (%)    |         |
| <b>Age, mean <math>\pm</math> SD</b> |                             |        |                         |        |         |
| <6 years                             | 7333                        | (20.0) | 7321                    | (20.0) | 0.012   |
| 6–12 years                           | 15450                       | (42.2) | 15973                   | (43.7) |         |
| 13–18 years                          | 13805                       | (37.7) | 13294                   | (36.3) |         |
| <b>Gender</b>                        |                             |        |                         |        |         |
| Female                               | 17534                       | (47.9) | 17496                   | (47.8) | 0.779   |
| Male                                 | 19054                       | (52.1) | 19092                   | (52.2) |         |
| <b>Comorbidities</b>                 |                             |        |                         |        |         |
| Atopic dermatitis                    | 1071                        | (2.9)  | 1113                    | (3.0)  | 0.362   |
| Chronic rhinitis                     | 11967                       | (32.7) | 11977                   | (32.7) | 0.937   |
| Sinusitis                            | 1708                        | (4.7)  | 1751                    | (4.8)  | 0.454   |
| Nasal polyps                         | 65                          | (0.2)  | 59                      | (0.2)  | 0.590   |

AR: allergic rhinitis; SD: standard deviation.

**Table 2** The risk of gastroesophageal reflux disease (GERD) between non-AR cohort and AR cohort.

|                         | GERD number | Per 1000 person-year | Adjusted HR <sup>a</sup> | (95% CI)    | p value |
|-------------------------|-------------|----------------------|--------------------------|-------------|---------|
| <b>Overall</b>          |             |                      |                          |             |         |
| Non-AR cohort           | 620         | 1.7                  |                          |             |         |
| AR cohort               | 1152        | 3.3                  | 1.91                     | (1.73–2.11) | <0.001  |
| <b>Age</b>              |             |                      |                          |             |         |
| <b>&lt; 6 years old</b> |             |                      |                          |             |         |
| Non-AR cohort           | 22          | 0.3                  | 1                        |             |         |
| AR cohort               | 58          | 0.8                  | 2.68                     | (1.64–4.38) | <0.001  |
| <b>6–12 years old</b>   |             |                      |                          |             |         |
| Non-AR cohort           | 178         | 1.2                  | 1                        |             |         |
| AR cohort               | 350         | 2.3                  | 1.99                     | (1.66–2.38) | <0.001  |
| <b>13–18 years old</b>  |             |                      |                          |             |         |
| Non-AR cohort           | 420         | 3.2                  | 1                        |             |         |
| AR cohort               | 744         | 5.9                  | 1.86                     | (1.65–2.1)  | <0.001  |

<sup>a</sup> Adjusted age, gender, and comorbidities.

AR: allergic rhinitis; GERD: gastroesophageal reflux disease; HR: hazard ratio; CI: confidence intervals.

age, gender, and comorbidities were similar between the AR cohort and the non-AR cohort (Table 1).

### The risk of GERD development in children with AR

The AR cohort and non-AR cohort were followed an average follow-up duration of 9.64 years, and 9.74 years, 1152 (3.15%) and 620 (1.69%) of two cohorts developed GERD within 10 years, respectively. The average duration of GERD development between non-AR cohort and AR cohort were  $7.10 \pm 2.02$  and  $7.00 \pm 2.11$  years, respectively. There was no statistically significant difference in different age stratification. The Kaplan–Meier analysis of the cumulative incidence of GERD demonstrated it to be significantly higher for the AR cohort than for the non-AR cohort in different age stratification (Fig. 1). After adjusted age, gender, and comorbidities, Cox proportional hazard regression analysis revealed that AR cohort was 91% more likely to develop GERD than non-AR cohort (adjusted HR

1.91, 95% CI = 1.73–2.11,  $p < 0.001$ ). The increased risk of GERD remained significant after adjusting for potential co-variables in different age stratification (<6 years old: adjusted HR 2.68, 95% CI = 1.64–4.38,  $p < 0.001$ ; 6–12 years old: adjusted HR 1.99, 95% CI = 1.66–2.38,  $p < 0.001$ ; 13–18 years old: adjusted HR 1.86, 95% CI = 1.65–2.21,  $p < 0.001$ ) (Table 2).

### The possible factors of GERD development in children with AR

After adjusted age, gender, comorbidities, there was associated risk factors with increased risk of GERD, followed by age (<6 years old as reference group, 6–12 years old: adjusted HR 2.93, 95% CI = 2.22–3.88,  $p < 0.001$ ; 13–18 years old: adjusted HR 7.18, 95% CI = 5.97–10.2,  $p < 0.001$ ), gender (female as reference group, adjusted HR = 0.70, 95% CI 0.62–0.79,  $p < 0.001$ ), chronic sinusitis

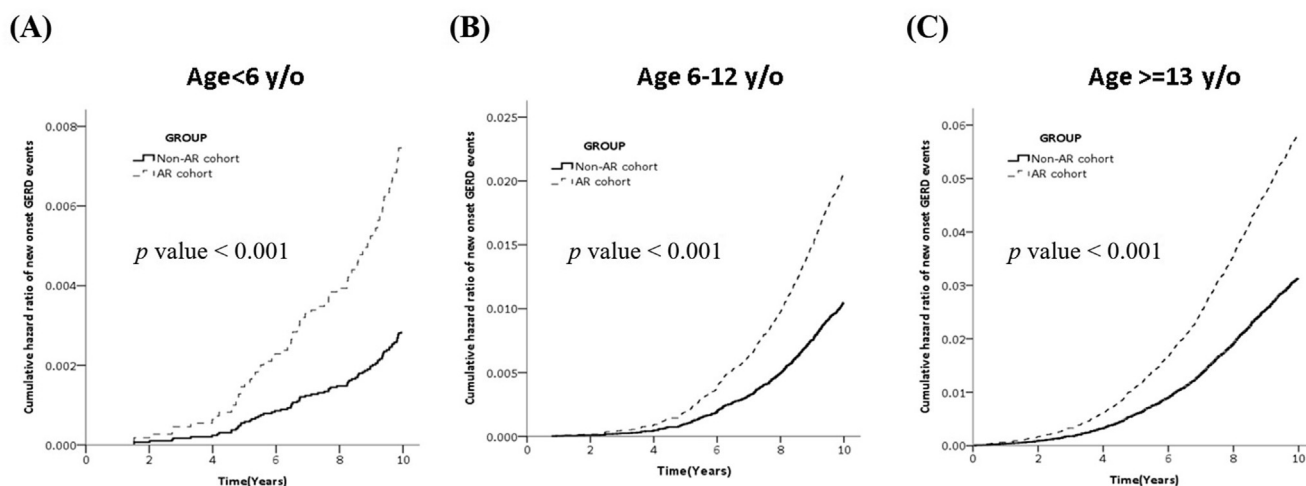


**Figure 1.** The cumulative hazard rates of GERD development in AR and non-AR children without asthma. The cumulative hazard rates of GERD development among AR children and the non-AR children without asthma in (a) age less than 6 years, (b) age between 6 and 12 years, and (c) age between 13 and 18 years.

**Table 3** The possible risk factors of gastroesophageal reflux disease in children with AR.

|                      | GERD number | (%)   | Adjusted HR <sup>a</sup> | (95% CI)    | p value |
|----------------------|-------------|-------|--------------------------|-------------|---------|
| <b>Age, years</b>    |             |       |                          |             |         |
| <6                   | 58          | (0.8) | 1.00                     |             |         |
| 6–12                 | 350         | (2.2) | 2.93                     | (2.22–3.88) | <0.001  |
| 13–18                | 744         | (5.6) | 7.81                     | (5.97–10.2) | <0.001  |
| <b>Gender</b>        |             |       |                          |             |         |
| Female               | 650         | (3.7) | 1.00                     |             |         |
| Male                 | 502         | (2.6) | 0.70                     | (0.62–0.79) | <0.001  |
| <b>Comorbidities</b> |             |       |                          |             |         |
| Atopic dermatitis    |             |       |                          |             |         |
| No                   | 1116        | (3.1) | 1.00                     |             |         |
| Yes                  | 36          | (3.2) | 1.11                     | (0.80–1.56) | 0.506   |
| Chronic rhinitis     |             |       |                          |             |         |
| No                   | 755         | (3.1) | 1.00                     |             |         |
| Yes                  | 397         | (3.3) | 1.20                     | (1.06–1.35) | 0.003   |
| Sinusitis            |             |       |                          |             |         |
| No                   | 1080        | (3.1) | 1.00                     |             |         |
| Yes                  | 72          | (4.1) | 1.26                     | (0.99–1.60) | 0.055   |
| Nasal polyps         |             |       |                          |             |         |
| No                   | 1150        | (3.1) | 1.00                     |             |         |
| Yes                  | 2           | (3.4) | 1.06                     | (0.26–4.25) | 0.932   |

<sup>a</sup> Adjusted age, gender, and comorbidities.

AR: allergic rhinitis; GERD: gastroesophageal reflux disease; HR: hazard ratio; CI: confidence intervals.

(adjusted HR 1.20, 95% CI = 1.06–1.35,  $p = 0.003$ ), but there was no statistically significant association with atopic dermatitis, rhinitis, and nasal polyps (Table 3).

### The interaction between AR and asthma on GERD development in children

Fig. 2 showed Kaplan–Meier analysis of the cumulative incidence of GERD demonstrated it to be significantly higher for the AR(+)/asthma(+) group than AR(–)/

asthma(–) group in different age stratification (log-rank test,  $p < 0.001$ ). Table 4 showed the interaction between AR and asthma on GERD development in children. the increased risk of GERD remained significant after adjusting for potential co-variables in different age stratification in AR(+)/asthma(+) group (<6 years old: adjusted HR 2.74, 95% CI = 1.55–4.82,  $p < 0.001$ ; 6–12 years old: adjusted HR 2.04, 95% CI = 1.61–2.59,  $p < 0.001$ ;  $\geq 13$  years old: adjusted HR 1.99, 95% CI = 1.65–2.40,  $p < 0.001$ ), and in AR(+)/asthma(–) group (<6 years old: adjusted HR 2.53, 95% CI = 1.34–4.75,  $p = 0.004$ ; 6–12 years old: adjusted

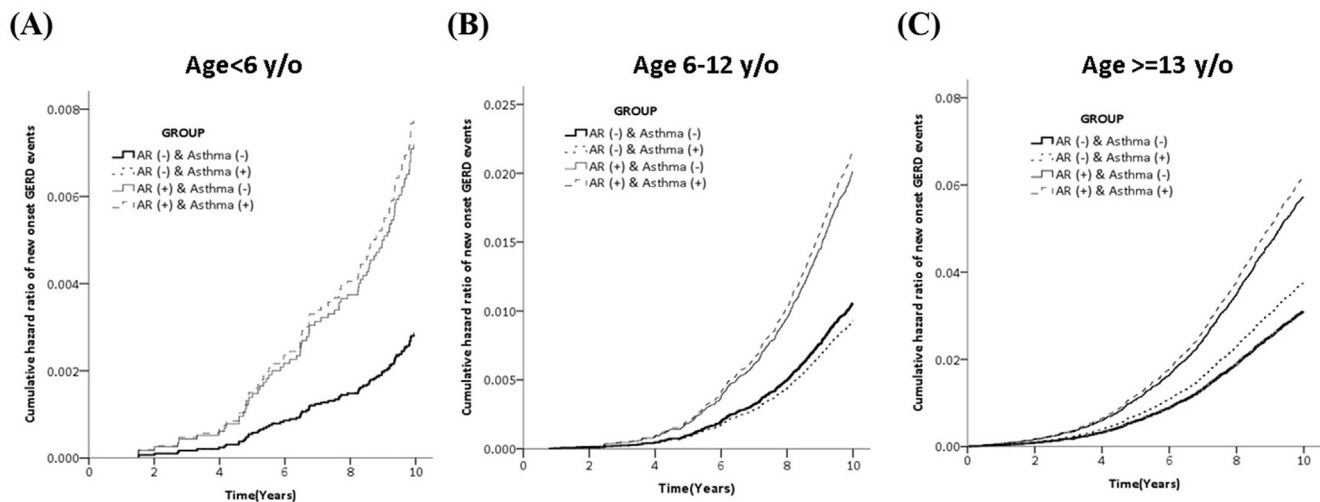


**Figure 2.** The cumulative hazard rates of GERD development in AR and non-AR children with/without asthma. The cumulative hazard rates of GERD development among AR children and the non-AR children with/without asthma in (a) age less than 6 years, (b) age between 6 and 12 years, and (c) age between 13 and 18 years.

**Table 4** The risk of GERD in the interaction between AR and asthma children.

|                         |             | GERD number | Per 1000 person-year | Adjusted HR <sup>a</sup> | (95% CI)    | p value |
|-------------------------|-------------|-------------|----------------------|--------------------------|-------------|---------|
| <b>Overall</b>          |             |             |                      |                          |             |         |
| AR (−) & Asthma (−)     | (n = 32960) | 575         | 1.8                  | 1.00                     |             |         |
| AR (−) & Asthma (+)     | (n = 3628)  | 45          | 1.3                  | 0.97                     | (0.72–1.32) | 0.875   |
| AR (+) & Asthma (−)     | (n = 23816) | 840         | 3.7                  | 1.90                     | (1.71–2.12) | <0.001  |
| AR (+) & Asthma (+)     | (n = 12772) | 312         | 2.5                  | 1.95                     | (1.70–2.24) | <0.001  |
| <b>&lt; 6 years old</b> |             |             |                      |                          |             |         |
| AR (−) & Asthma (−)     | (n = 6035)  | 18          | 0.3                  | 1.00                     |             |         |
| AR (−) & Asthma (+)     | (n = 1298)  | 4           | 0.3                  | 1.01                     | (0.34–3.00) | 0.980   |
| AR (+) & Asthma (−)     | (n = 2826)  | 21          | 0.8                  | 2.53                     | (1.34–4.75) | 0.004   |
| AR (+) & Asthma (+)     | (n = 4495)  | 37          | 0.8                  | 2.74                     | (1.55–4.82) | <0.001  |
| <b>6–12 years old</b>   |             |             |                      |                          |             |         |
| AR (−) & Asthma (−)     | (n = 13869) | 164         | 1.2                  | 1.00                     |             |         |
| AR (−) & Asthma (+)     | (n = 1581)  | 14          | 0.9                  | 0.88                     | (0.50–1.52) | 0.649   |
| AR (+) & Asthma (−)     | (n = 10276) | 229         | 2.3                  | 1.90                     | (1.55–2.32) | <0.001  |
| AR (+) & Asthma (+)     | (n = 5697)  | 121         | 2.2                  | 2.04                     | (1.61–2.59) | <0.001  |
| <b>≥13 years old</b>    |             |             |                      |                          |             |         |
| AR (−) & Asthma (−)     | (n = 13056) | 393         | 3.1                  | 1.00                     |             |         |
| AR (−) & Asthma (+)     | (n = 749)   | 27          | 3.8                  | 1.21                     | (0.82–1.78) | 0.336   |
| AR (+) & Asthma (−)     | (n = 10714) | 590         | 5.8                  | 1.85                     | (1.62–2.10) | <0.001  |
| AR (+) & Asthma (+)     | (n = 2580)  | 154         | 6.3                  | 1.99                     | (1.65–2.40) | <0.001  |

<sup>a</sup> Adjusted age, gender, and comorbidities.

n: numbers; GERD: gastroesophageal reflux disease; AR: allergic rhinitis; HR: hazard ratio; CI: confidence intervals.

HR 1.90; 95% CI = 1.55–2.32,  $p < 0.001$ ;  $\geq 13$  years old: adjusted HR, 1.85; 95% CI = 1.62–2.10,  $p < 0.001$ ), but not in AR(−)/asthma(+) group (<6 years old: adjusted HR 1.01, 95% CI = 0.34–3.00,  $p = 0.980$ ; 6–12 years old: adjusted HR 0.88, 95% CI = 0.50–1.52,  $p = 0.649$ ;  $\geq 13$  years old: adjusted HR 1.21, 95% CI = 0.82–1.78,  $p = 0.336$ ), as the AR(−)/asthma(−) is the reference group (Table 4).

## Discussion

GERD is common in children with allergic asthma and may be present with or without related symptoms. The common signs and symptoms of GERD include burning sensation in chest, difficulty swallowing, Regurgitation of food or sour liquid and sensation of a lump in your throat. The esophageal symptoms of GERD have been well recognized; however, there are extra-esophageal manifestations of GERD, which include asthma, chronic cough, laryngitis and sinusitis. Extra-esophageal manifestations of GERD have received increasing attention over the last decade, especially respiratory symptoms, because of the prevalent co-occurrence with GERD. Several atopic disorders, such as asthma, AR, atopic dermatitis, and eosinophilic esophagitis are common comorbidities in patients with GERD implicate the nature of the relationship that may exist between GERD and atopic disorders.<sup>4</sup> The prevalence of GERD in asthma ranges from 30% to 90%, compared to an average of 24% in controls.<sup>19</sup> However, the causality of GERD in patients with asthma is not established and GERD treatment yielded inconsistent effects. Some other results of anti-reflux therapy of GERD on pulmonary outcome are also showed inconsistent and contradictory.<sup>20</sup> A subset of asthma patients with documented GERD may experience improved

asthma control following appropriate treatment of GERD. Asthma and rhinitis are common allergic and respiratory diseases with a marked predominance in children with Th2-driven prominent nasal allergic inflammation.<sup>12,13,15</sup> Asthma has been considered risk factors to develop GERD and is the important comorbidity of AR. However, the effect of AR on GERD development is still not clear. We tried to evaluate the effect of childhood AR with or without asthma on the development of GERD.

In the present study, the hazard ratio is significantly higher in AR than that in control group in all age group to develop GERD later. The younger age group (less than 6 years old) had a highest risk between AR and non-AR group when compared with other age group. In AR population, the older age group (13–18 years old) had a very high incidence when compared with other age group in all AR patients. Male AR children has a lower risk to develop GERD than female AR children. Further studies are needed to confirm these data and examine possible determinants and underlying mechanisms. Within the comorbidities of AR, only chronic rhinitis has a significantly higher adjusted HR to develop GERD. However, the association between the development of GERD and the previous history of asthma was also not significant in the present study (Fig. 1). As AR alone, the effect of AR with or without asthma on development of GERD is obvious. Asthma has several different comorbidities. The most common co-morbidities in severe asthma include chronic rhinosinusitis, nasal polyposis, AR, dysfunctional breathing, vocal cord dysfunction, anxiety and depression, obesity, obstructive sleep apnoea syndrome and GERD.<sup>21,22</sup> Asthma and AR have been considered as similar allergic airway diseases in different location because they share with similar histology and pathophysiology.

With the rising incidence of asthma and AR, there is increasing interest in identifying how GERD impacts asthma

development and related therapy. There were no previous studies examined the simultaneous presence of AR and asthma on the development of GERD in children. We tried to analyze the interaction between AR and asthma on GERD in this study (Table 4). The data shows a weakly additive effect of asthma on AR to develop to GERD in child population. AR with asthma children (shown as AR(+)/asthma(+)) had the highest risk of GERD development, then are the AR(+)/asthma(−) groups and the AR(−)/asthma(+) group in all age group, as the AR(−)/asthma(−) is the reference group. The data of the interaction between AR and asthma on GERD showed that only the positive AR group as well as the coexistence of AR and asthma group increased the risk of GERD development, especially in age less than 6 years old group (Table 4). The risk on GERD development is higher in AR with or without asthma in age less than 6 years old group than in other age groups. Therefore, the effect of AR on the development of GERD is strongest in very young age group. This finding suggested that the children in age less than 6 years old group with AR symptoms should be clearly diagnosed by physician and treated early to reduce the risk of GERD development.

Otherwise, we also tried to adjust asthma to specify whether asthma is associated with the development of GERD (Table 4). In the children with asthma, AR(+)/asthma(+) group had significantly higher risk for GERD development than AR(−)/asthma(+) group. In the children without asthma, AR(+)/asthma(−) group still had significantly higher risk for GERD development than AR(−)/asthma(−) group. In contrast, in the children with AR, the risks for GERD development were both significantly higher in the AR(+)/asthma(+) group and the AR(+)/asthma(−) group, compared to the reference group (AR(−)/asthma(−)). In the children without AR, the risk for GERD development was no significant difference between AR(−)/asthma(+) group and AR(−)/asthma(−) group. The results seemed to indicate that AR but not asthma is significantly associated with the development of GERD in childhood.

Transient lower esophageal sphincter relaxation (TLESR) is the most common mechanism underlying acid reflux in patients with GERD.<sup>23</sup> AR patients may increase frequency of swallowing due to throat itching and posterior nasal dripping with nasal discharge.<sup>24</sup> The frequent swallowing may exacerbate the reflux by increased TLESRs. The other potential explanation is that the inflammatory response with GERD could be further aggravated in the setting of preexisting eosinophilic inflammation because of atopic airway disease in the pathogenesis of AR. The allergic effects of AR on nasal mucosa may give rise to similar effects on laryngeal mucosa including congestion, edema and excessive mucous secretion leading to symptoms of laryngopharyngeal reflux, a subgroup of GERD.<sup>25</sup> GERD may also be caused by the release of histamine from mast cells, which can promote the onset of this disease by exacerbating lower esophageal sphincter contractions.<sup>26</sup> Eosinophils, one of the key components of the allergic inflammation, are also discovered in esophageal mucosa of GERD patients.<sup>27,28</sup> The mutual allergic inflammation in response to an allergen or allergens with high cross-reactivity that come in contact with both mucosal membranes could be the drive for atopic diseases and GERD in AR cases.

Our studies had still several limitations in that we did not consider confounding by obesity, food allergy, smoking,

urticaria, socio-economic status, and region of residence. Moreover, the tools for exact diagnosis of AR and GERD may be dissimilar, thus under-diagnosis or over-diagnosis could lead to inaccurate interpretations. A previous study showed the prevalence of GERD in asthma ranges from 30% to 90%, compared to an average of 24% in controls.<sup>19</sup> In another study, the prevalence of GERD seemed increase by age.<sup>29</sup> The prevalence was 3.2% among children under 10 years of age. That prevalence among all subjects under 20 years of age was 4.4%, and 11.6% in adults. In our study, The diagnosis of AR and GERD is according to ICD-9 code. The prevalence rates of GERD were 3.15% and 1.69% in AR and non-AR cohorts, respectively. The prevalence rates in different studies would be varied due to different population (asthma patients, general population, or AR children) and different tools for exact diagnosis of GERD.

In conclusion, our results provide evidences that AR with or without asthma, have an increased risk factor for developing new-onset GERD in children. Male AR children have a lower risk to develop GERD than female AR children. Asthma may not increase the risk of GERD other than allergic factors shared with AR. Because the size for the subgroup of AR (−)/asthma (+) is relatively small, the precise interaction and causal relation between AR, asthma, and GERD is worth further investigation.

## Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

## Acknowledgments

The study was supported partially by grants the Ministry of Science and Technology of the Republic of China (MOST107-2635-B-037-003-), the Changhua Christian Hospital and Kaohsiung Medical University Research Foundation (103-CCH-KMU-005), and the Research Center for Environmental Medicine, Kaohsiung Medical University from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

## References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49:498–547.
2. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54:710–7.
3. de Benedictis FM, Bush A. Respiratory manifestations of gastro-oesophageal reflux in children. *Arch Dis Child* 2018;103:292–6.
4. Mahdavinia M, Bishehsari F, Hayat W, Codispoti CD, Sarrafi S, Husain I, et al. Prevalence of allergic rhinitis and asthma in patients with chronic rhinosinusitis and gastroesophageal reflux disease. *Ann Allergy Asthma Immunol* 2016;117:158–162.e1.

5. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–43.
6. Rameschandra S, Acharya V, Kunal, Vishwanath T, Ramkrishna A, Acharya P. Prevalence and spectrum of gastroesophageal reflux disease in bronchial asthma. *J Clin Diagn Res* 2015;**9**:Oc11–4.
7. Kim JT, Kim HS, Chun YH, Yoon JS, Kim HH. Effect of multi-ethnicity and ancestry on prevalence of allergic disease. *J Microbiol Immunol Infect* 2020;**53**(4):640–6.
8. Tsao SM, Ko YK, Chen MZ, Chiu MH, Lin CS, Lin MS, et al. A survey of allergic rhinitis in Taiwanese asthma patients. *J Microbiol Immunol Infect* 2011;**44**:139–43.
9. van den Nieuwenhof L, Schermer T, Bosch Y, Bousquet J, Heijdra Y, Bor H, et al. Is physician-diagnosed allergic rhinitis a risk factor for the development of asthma? *Allergy* 2010;**65**:1049–55.
10. Yu CL, Huang WT, Wang CM. Treatment of allergic rhinitis reduces acute asthma exacerbation risk among asthmatic children aged 2–18 years. *J Microbiol Immunol Infect* 2019;**52**:991–9.
11. Lin YC, Chen YC, Kuo CH, Chang YH, Huang HY, Yeh WJ, et al. Antibiotic exposure and asthma development in children with allergic rhinitis. *J Microbiol Immunol Infect* 2019. <https://doi.org/10.1016/j.jmii.2019.02.003>. S1684-1182(18)30215-9. [Epub ahead of print].
12. Forno E, Gogna M, Cepeda A, Yanez A, Sole D, Cooper P, et al. Asthma in Latin America. *Thorax* 2015;**70**:898–905.
13. Dennis RJ, Caraballo L, Garcia E, Rojas MX, Rondon MA, Perez A, et al. Prevalence of asthma and other allergic conditions in Colombia 2009–2010: a cross-sectional study. *BMC Pulm Med* 2012;**12**:17.
14. Wang YH, Lue KH. Association between sensitized to food allergens and childhood allergic respiratory diseases in Taiwan. *J Microbiol Immunol Infect* 2019. <https://doi.org/10.1016/j.jmii.2019.01.005>. S1684-1182(18)30181-6. [Epub ahead of print].
15. Arasi S, Pajno GB, Lau S, Matricardi PM. Local allergic rhinitis: a critical reappraisal from a paediatric perspective. *Pediatr Allergy Clin Immunol* 2016;**27**:569–73.
16. Randel A. AAP releases guideline for the management of gastroesophageal reflux in children. *Am Fam Physician* 2014;**89**:395–7.
17. Šofranac M. Correlation between allergic rhinitis, asthma, and atopic dermatitis in children. *Pediatrics* 2008;**121**:S91–S.
18. Hoffmans R, Wagemakers A, van Drunen C, Hellings P, Fokkens W. Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment. *PLoS One* 2018;**13**:e0192330.
19. Broers C, Tack J, Pauwels A. Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. *Aliment Pharmacol Ther* 2018;**47**:176–91.
20. Naik RD, Vaezi MF. Extra-esophageal gastroesophageal reflux disease and asthma: understanding this interplay. *Expert Rev Gastroenterol Hepatol* 2015;**9**:969–82.
21. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. *Respirology* 2017;**22**:651–61.
22. Wong IW, Rees G, Greiff L, Myers JC, Jamieson GG, Wormald PJ. Gastroesophageal reflux disease and chronic sinusitis: in search of an esophageal-nasal reflex. *Am J Rhinol Allergy* 2010;**24**:255–9.
23. Iwakiri K, Hoshino S, Kawami N. Transient lower esophageal sphincter relaxation. *Nihon Rinsho* 2016;**74**:1343–8.
24. Loehrl TA, Smith TL, Darling RJ, Torrico L, Prieto TE, Shaker R, et al. Autonomic dysfunction, vasomotor rhinitis, and extra-esophageal manifestations of gastroesophageal reflux. *Otolaryngol Head Neck Surg* 2002;**126**:382–7.
25. Jackson-Menaldi CA, Dzul AI, Holland RW. Allergies and vocal fold edema: a preliminary report. *J Voice* 1999;**13**:113–22.
26. Eren E, Arslanoglu S, Aktas A, Kopar A, Ciger E, Onal K, et al. Factors confusing the diagnosis of laryngopharyngeal reflux: the role of allergic rhinitis and inter-rater variability of laryngeal findings. *Eur Arch Oto-Rhino-Laryngol* 2014;**271**:743–7.
27. Pope SM, Brandt EB, Mishra A, Hogan SP, Zimmermann N, Matthaei KI, et al. IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. *J Allergy Clin Immunol* 2001;**108**:594–601.
28. Mahdavinia M, Carter RG, Ocampo CJ, Stevens W, Kato A, Tan BK, et al. Basophils are elevated in nasal polyps of patients with chronic rhinosinusitis without aspirin sensitivity. *J Allergy Clin Immunol* 2014;**133**:1759–63.
29. Okimoto E, Ishimura N, Morito Y, Mikami H, Shimura S, Uno G, et al. Prevalence of gastroesophageal reflux disease in children, adults, and elderly in the same community. *J Gastroenterol Hepatol* 2015;**30**:1140–6.