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Review Article

Comorbidity of allergic rhinitis and asthma in children: a meta-analysis

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Abstract: Objective: To perform a meta-analysis to study the rate of comorbidity of asthma and allergic rhinitis (AR) in children. Methods: A literature search of Chinese and English biomedical databases was conducted from 2007 to 2017 for clinical studies on the relationship between AR and asthma in children. Inclusion and exclusion criteria were identified for the study. Relevant data of the included studies were extracted and all studies were graded. The retrieved data were examined by a test of heterogeneity and Hardy-Weinberg Equilibrium. A fixed effects model was therefore used to pool the odds ratio (OR). Publication bias was assessed using REVMAN5.3. Results: We obtained 14 studies that met all of the inclusion criteria for this analysis, of which 9 were published in China and 5 in other countries. Of these studies, 8 were graded as A and 6 as B. The results from REVMAN5.3 showed that the studies showed no significant heterogeneity (P>0.05). A fixed effects model was then selected for this analysis. For the Chinese children in this analysis, the pooled OR was 3.007 with 95% confidence interval (CI)=1.705-3.349, test for overall effect, Z=11.83, P<0.0001; for the children in other countries in this analysis, the pooled OR was 3.013 with 95% CI=1.687-3.305, test for overall effect, Z=10.56, P<0.0001. This indicated that asthma was an important causative factor of AR for children at home and abroad. Therefore, the study was of significance. The funnel plot suggested that there was no significant publication bias in the meta-analysis. AR was more prevalent in Chinese children with asthma than that in children with asthma in other countries. Conclusion: There was a positive correlation between AR and asthma in children. Children with AR has a higher rate of suffering asthma than those with non-allergic rhinitis.

Keywords: Children, allergic rhinitis, asthma, meta-analysis

Introduction

Allergic rhinitis (AR) and asthma are both common respiratory allergic conditions in children, and their prevalence has been growing in recent years. Since AR and asthma are both inflammatory conditions of the airways, there are a growing number of researchers and doctors who have found the close relationship between them [1]. Previous studies showed that AR and asthma often occurred concomitantly, which indicated that most AR patients suffered asthma, or vice versa [2]. The two conditions are similar in pathogenesis and clinical features, though they affect different parts of the respiratory tract. For this reason, AR and asthma often occur concomitantly or in a successive way [3]. Therefore, we searched biomedical databases for clinical studies on the relationship between AR and asthma. A total of 14 studies published between 2007 and 2017 were included for the meta-analysis. This analysis on the clinical features of AR and asthma would provide a better understanding for physicians towards the relationship and differences between the two conditions, helping them in the treatment of such conditions.

Materials and methods

Search strategy

A literature search of relevant clinical studies published from 2007 to 2017 was conducted. Relevent studies were identified from Pubmed, Medline, Springer, Embase, Science and Cochrane Library, and four Chinese biomedical databases including VIP, Wanfang Data, CNKI and CBM. Chinese search terms used were “bi yan”, “guo min xing bi yan”, “bian ying xing bi yan”, “hua fen zheng”, “xiao chuan”, “bian ying xing xiao chuan”, “er tong/qing shao nian/xiao er”,

Table 1. Overview of the included studies

Study	Age Range (year)	Diagnostic Criteria	Asthma (n)	AR with Asthma (n)	Quality Assessment
He et al., 2008 [4]	7-15	ARIA	467	152	A
Xiao, 2009 [5]	3-12	Scheme and Guideline	40	18	B
Chen, 2010 [6]	4-13	Scheme and Guideline	44	19	B
Yang et al., 2011 [7]	0-13	Scheme and Guideline	75	26	A
Chen et al., 2015 [8]	3-7	Scheme and Guideline	802	312	A
Lu et al., 2008 [9]	13-14	ARIA	2,104	738	A
Ma et al., 2013 [10]	0-14	ISAAC	319	111	B
Xu et al., 2014 [11]	7-11	Scheme and Guideline	151	38	B
Wang et al., 2007 [12]	7-11	ARIA	131	43	A
Garciaaymerich et al., 2015 [13]	3-10	ARIA	2,107	605	B
Westman et al., 2012 [14]	0-4	ISAAC	389	92	A
Yamauchi et al., 2009 [15]	0-16	ARIA	1,935	611	A
Ait-Khaled et al., 2007 [16]	13-14	ISAAC	6,385	2,014	B
Burgess et al., 2007 [17]	0-7	ISAAC	711	213	A

Note: ARIA refers to Allergic Rhinitis and its Impact on Asthma; ISAAC refers to International Study of Asthma and Allergies in Childhood; AR refers to allergic rhinitis; Scheme refers to Diagnostic and treatment principle for allergic rhinitis and a recommended scheme and Guideline refers to Guideline for the diagnosis and management of pediatric asthma.

"zhi min xiao chuan". English search terms used were "Rhinitis", "Allergic", "Asthma", "children/childhood/adolescent/pediatric", "Allergic asthma", "Hay fever", "Sensitized asthma" (all were included in Medical Subject Headings). The search was conducted with the use of text words and subject headings. Reference lists of the included articles were manually searched to find additional studies. The reference period for the literature search was from January 2007 to December 2017. Title was searched in CSCD, SCI and SCIE on the basis of the Boolean search string, which was ((Rhinitis OR Allergic OR Asthma OR Allergic asthma OR Hay fever OR Sensitized asthma) and (children OR childhood OR adolescent OR pediatric)). The filter was activated to include only studies published between January 2007 and December 2017.

Inclusion and exclusion criteria

To fulfill the analysis requirement and to reduce systematic and random errors, the eligibility of the retrieved studies was evaluated according to the inclusion and exclusion criteria.

Inclusion criteria: Studies adopted the widely applied clinical diagnostic criteria for AR and asthma; studies revealed the relationship between AR and asthma in children; studies based on randomized controlled trials and with the number of participants in each group; independent studies that had odds ratio (OR) and 95% confidence interval (CI); methods used in the study met the requirements of epidemiology; studies with appropriate design and statistical analysis; subjects in the study were under the age of 16.

Exclusion criteria: Studies with data that could not be imported to Revman software; duplicate studies; retrospective studies; studies of inferior quality; studies with unqualified statistical results.

Data extraction

Two reviewers independently screened the retrieved studies according to the inclusion and exclusion criteria, extracted data in a standardized spreadsheet and assessed the methodological quality of the included studies. The extracted data were reviewed by the two reviewers. All disagreements in data extraction were resolved by discussing according to the original study.

Quality assessment

Two researchers independently assessed the quality and bias risks of the included studies according to Combie criteria for cross-sectional studies, which contain the following seven domains: the study's design is scientific; the data collection strategy is reasonable; the research reports sample response rates; the

Table 2. The results of skin prick test in Chinese children

Study	Group	Cases	Dust mite positive cases (n, %)	Pollen positive cases (n, %)
He et al., 2008 [4]	Asthma (n)	467	422 (90.36)	424 (90.79)
	AR with Asthma (n)	152	138 (90.79)	124 (81.58)
Xiao, 2009 [5]	Asthma (n)	40	35 (87.50)	34 (85.00)
	AR with Asthma (n)	18	16 (88.89)	17 (94.44)
Chen, 2010 [6]	Asthma (n)	44	38 (86.36)	36 (81.82)
	AR with Asthma (n)	19	17 (89.47)	18 (94.74)
Yang et al., 2011 [7]	Asthma (n)	75	66 (88.00)	64 (85.33)
	AR with Asthma (n)	26	24 (92.31)	23 (88.46)
Chen et al., 2015 [8]	Asthma (n)	802	718 (89.53)	722 (90.02)
	AR with Asthma (n)	312	287 (91.99)	292 (93.59)
Lu et al., 2008 [9]	Asthma (n)	2,104	1,870 (88.88)	1,882 (89.45)
	AR with Asthma (n)	738	667 (90.38)	681 (92.28)
Ma et al., 2013 [10]	Asthma (n)	319	265 (83.07)	272 (85.27)
	AR with Asthma (n)	111	98 (88.29)	100 (90.09)
Xu et al., 2014 [11]	Asthma (n)	151	122 (80.79)	124 (82.12)
	AR with Asthma (n)	38	35 (92.10)	34 (89.47)
Wang et al., 2007 [12]	Asthma (n)	131	110 (83.97)	112 (85.50)
	AR with Asthma (n)	43	36 (83.72)	38 (88.37)

Note: AR refers to allergic rhinitis.

Table 3. The results of skin prick test in children of other countries

Study	Group	Cases	Dust mite positive cases (n, %)	Pollen positive cases (n, %)
Garciaaymerich et al., 2015 [13]	Asthma (n)	131	115 (87.79)	109 (83.21)
	AR with Asthma (n)	43	39 (90.70)	37 (86.05)
Westman et al., 2012 [14]	Asthma (n)	2,107	1,882 (89.32)	1,843 (87.47)
	AR with Asthma (n)	645	584 (90.54)	588 (91.16)
Yamauchi et al., 2009 [15]	Asthma (n)	1,935	1,702 (87.96)	1,711 (88.42)
	AR with Asthma (n)	674	611 (90.65)	608 (90.21)
Ait-Khaled et al., 2007 [16]	Asthma (n)	6,385	5,703 (89.32)	5,726 (89.68)
	AR with Asthma (n)	2,272	2,057 (90.54)	2,049 (90.18)
Burgess et al., 2007 [17]	Asthma (n)	711	611 (85.94)	624 (87.76)
	AR with Asthma (n)	235	215 (91.49)	218 (92.77)

Note: AR refers to allergic rhinitis.

representativeness of samples is very good; the research purpose and method are reasonable; the study reports the statistical power of the data and the study has appropriate statistical analysis. Every domain was judged by Yes, No or Unclear. Yes stands for 1 point, No stands for 0 point and Unclear stands for 0.5 point. The total score of this assessment was 7.0 point. Those studies with scores of 6.0-7.0 were graded as A; those studies with scores of 4.0-5.5 were graded as B and those studies with scores of lower than 4.0 were graded as C.

Statistical analysis

Since the data of the included studies were all binary data, pooled ORs were calculated in the meta-analysis. The retrieved data were examined by a test of heterogeneity and Hardy-Weinberg Equilibrium. If there was no heterogeneity among studies, we used a fixed effects model to pool the ORs; otherwise, a random effects model was selected. The 95% CIs for count variables were calculated. $P<0.05$ was considered to be statistically significant.

Table 4. The relationship between AR and asthma in Chinese children

Study	Events (n)	Total (n)	Proportion	95% CI	W (random)
He et al., 2008 [4]	152	467	0.33	1.698-3.257	9.8%
Xiao, 2009 [5]	18	40	0.45	1.712-3.351	3.8%
Chen, 2010 [6]	19	44	0.43	1.704-3.126	11.4%
Yang et al., 2011 [7]	26	75	0.35	1.703-3.419	17.6%
Chen et al., 2015 [8]	312	802	0.39	1.685-3.057	18.7%
Lu et al., 2008 [9]	738	2,104	0.35	1.557-3.126	15.3%
Ma et al., 2013 [10]	111	319	0.35	1.715-3.213	9.7%
Xu et al., 2014 [11]	38	151	0.25	1.721-3.058	6.5%
Wang et al., 2007 [12]	43	131	0.33	1.664-3.027	7.2%
Random effects model		4133	0.36	1.705-3.349	100%

Note: AR refers to allergic rhinitis; CI refers to confidence interval; Heterogeneity: Chi^2=23.85, df=23 (P=0.36), I^2=9%. Test for overall effect: Z=11.83 (P<0.0001).

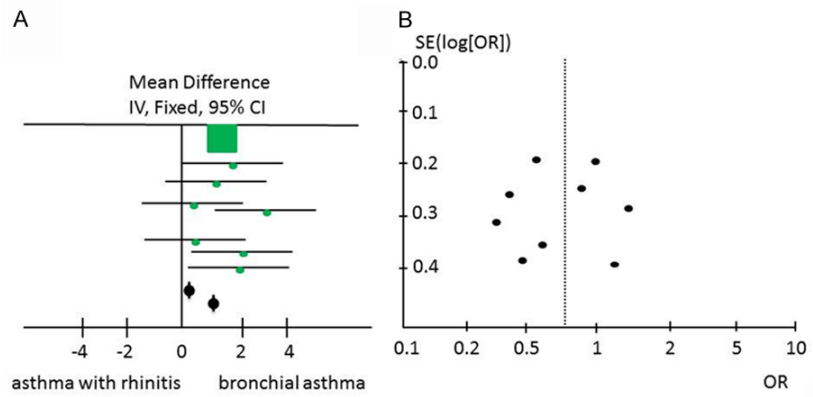

Figure 1. Comparison of AR and asthma in Chinese children. A: The forest plot on the relationship between asthma and AR in children. B: The funnel plot. AR refers to allergic rhinitis; CI refers to confidence interval; OR refers to odds ratio.

Publication bias was assessed using REVMAN5.3.

Results

Search results and quality assessment

A total of 487 studies were retrieved upon initial database search, of which 274 were published in Chinese and 213 in English. After deduplication, 292 studies were excluded in this study. The titles and abstracts of those studies were further screened against the inclusion and exclusion criteria. And 153 studies were excluded as irrelevant or unqualified studies. Finally, there were 14 studies met all of the inclusion criteria, of which 9 were published in China and 5 in other countries. Of these studies, 8 of them were graded A and 6 were graded B. See **Table 1** [4-17].

Results of skin prick test

Dust mite and pollen are the two most common allergens for patients with rhinitis. The results of skin prick test showed that for the Chinese children and children of other countries in this analysis, more than 80.00% of them with asthma or with asthma and concomitant AR were sensitized to pollen and dust mite. See **Tables 2** and **3** [4-17].

The relationship between AR and asthma in chinese children

Hardy-Weinberg Equilibrium was used to examine the 9 studies on Chinese children, and the results showed that these studies had collected representative samples (P> 0.05). The results from REVMAN5.3 demonstrated that these studies showed no significant heterogeneity (P>0.05). Therefore, a fixed effects model was used in this analysis. The pooled OR was 3.007, 95% CI=1.705-3.349 (P<0.05), indicating that asthma was a risk factor for AR. The study was of significance. See **Table 4**.

The relationship between AR and asthma in children was further analyzed. The forest plot showed that the results of horizontal lines of 95% CI were located to the right of the line of no effect, which proved that the presence of asthma would add to the risks of suffering AR. In the funnel plot, each dot represents an included study. The plot was not largely symmetric, suggesting the possibility of publication biases in the included studies. See **Figure 1**.

The relationship between AR and asthma in children of other countries

Hardy-Weinberg Equilibrium was used to examine the 5 studies on children of other countries,

Table 5. The relationship between AR and asthma in children of other countries

Study	Events (n)	Total (n)	Proportion	95% CI	W (random)
Garciaaymerich et al., 2015 [13]	605	2,107	0.29	1.698-3.341	16.2%
Westman et al., 2012 [14]	92	389	0.24	1.715-3.259	21.4%
Yamauchi et al, 2009 [15]	611	1,935	0.32	1.687-3.028	17.7%
Ait-Khaled et al., 2007 [16]	2,014	6,385	0.32	1.707-3.224	21.9%
Burgess et al., 2007 [17]	213	711	0.30	1.694-3.058	22.8%
Random effects model		11,527	0.294	1.687-3.305	100%

Note: AR refers to allergic rhinitis; CI refers to confidence interval; Heterogeneity: Chi^2=21.53, df=19 (P=0.41), I^2=8%. Test for overall effect: Z=10.56 (P<0.0001).

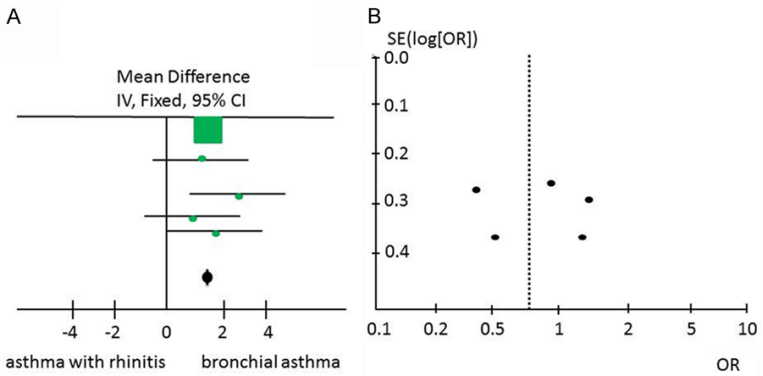

Figure 2. Comparison of AR and asthma in children of other countries. A: The forest plot on the relationship between asthma and AR in children. B: The funnel plot. AR refers to allergic rhinitis; CI refers to confidence interval; OR refers to odds ratio.

and the results showed that these studies had collected representative samples (P>0.05). The results from REVMAN5.3 showed that the studies showed no significant heterogeneity (P>0.05). Therefore, a fixed effects model was used in this analysis. The pooled OR was 3.013, 95% CI=1.687-3.305 (P<0.05), indicating that asthma was a risk factor for AR. The study was of significance. See **Table 5**.

The forest plot showed that the results of horizontal lines of 95% CI were located to the right of the line of no effect, which proved that the presence of asthma would add to the risks of suffering AR. In the funnel plot, each dot represents an included study. The plot was not largely symmetric, suggesting the possibility of publication biases in the included studies. See **Figure 2**.

Differences in incidence in different countries

The results showed that the prevalence of AR in Chinese children with asthma was 35.25% (1,457/4,133), and the prevalence of AR in children of other countries with asthma was 30.67% (3,535/11,527). This suggested that asthma with concomitant AR was more prevalent in Chinese children than in children of other countries (X^2=29.461, P<0.0001).

Discussion

Studies on asthma and AR showed that children with asthma often suffered AR and that the rate of comorbidity of asthma and AR was significantly higher in Chinese children than that in children of other countries [2, 18]. A previous study has identified environmental and genetic factors as causative factors of asthma, AR and other allergic diseases [19]. The worsened air quality in China in recent years might account for the difference in the rates of comorbidity between children in China and children of other countries [20].

Nasal mucosa offers the body the first line of defense against a wide range of invading pathogens [21]. Studies proved that functional changes of nasal mucosa occurred in children with AR would stimulate the airways. That would promote the activation of T cells and antigen-presenting cells (APCs), which would lead to airway hyperresponsiveness [21, 22]. Airway hyperresponsiveness would, in turn, result in bronchoconstriction by stimulating trigeminal sensory endings, leading to asthma [23]. Children with AR, characterized by nasal obstruction, usually breathes through mouth. In such cases, nasal mucosa cannot play its due role of protecting lower airways and the lung, aggravating AR and complicating the dis-

ease with asthma and other diseases [24]. Linneberg et al. conducted the bronchial challenge test in children with asthma and AR. The results showed that airway hyperresponsiveness occurred in 76.9% of children with AR, while this number was 94.9% in children with asthma. This showed the close relationship between AR and asthma [25]. AR and allergic asthma are manifestations of one disease entity. The coexistence of the two conditions means that the treatment of one condition also has significance for the prevention and control of another condition. Therefore, a holistic therapeutic approach for AR and asthma is recommended.

A meta-analysis adopts a statistical approach to combine the results from several studies of the same kind [26]. It is useful in deriving a pooled estimate closest to the unknown common truth, especially when the results of those studies are inconsistent or have no statistical significance. The 14 studies included in our analysis were all about AR and asthma, of which 9 were published in China and 5 in other countries. According to these studies, most of the children with asthma were complicated by AR, which indicated the strong association between the two conditions. In this study, all children with AR or asthma received skin prick test. The results showed that over 80.00% of the tested children were sensitized to dust mite and pollen. Georgopoulos et al. have demonstrated that dust mite and pollen are independent risk factors for asthma and AR [27]. This proved that the two conditions shared common allergens. According to the fixed effects model, the pooled OR was calculated as 3.007, 95% CI=1.705-3.349, which revealed the relationship between AR and asthma in children. Of the studies included in this analysis, all ORs crossed the Y-axis of the forest plot, indicating a close relationship between AR and asthma in children.

In conclusion, our study revealed a close relationship between asthma and AR. This will help physicians in the diagnosis of asthma and AR in children. Moreover, a therapeutic approach that combines the treatment of both AR and asthma appears to be effective and cost-efficient. Nevertheless, this study still has some limitations. First, children with AR and asthma were not classified according to gender or age. Second, though the analysis included studies over the past 10 years, environmental factors and the rapid development of allergic conditions would still contribute to the inherent biases of the results. Therefore, prospective analyses are warranted to study the relationship between AR and asthma.

Disclosure of conflict of interest

None.

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