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Original Article

Risk Factors and Comorbidities Associated With the Allergic Rhinitis Phenotype in Children According to the ARIA Classification

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ABSTRACT

Purpose: Data are lacking on the association between the allergic rhinitis (AR) phenotype and sensitization to specific allergens or bronchial hyperresponsiveness (BHR) in children. We here investigated risk factors and comorbidities, including sensitization to specific allergens and BHR, for the AR phenotype by AR and its Impact on Asthma (ARIA) classification in a general population-based birth cohort study.
Methods: We enrolled 606 children aged 7 years from the Panel Study of Korean Children. The AR phenotype was assigned in accordance with the ARIA classification in children. Skin prick tests and Provocholine provocation test were performed. Risk factors and comorbidities for AR phenotypes were then analyzed.

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Disclosure
There are no financial or other issues that might lead to conflict of interest.

Results: The prevalence of mild and moderate to severe AR in our study cohort was 37.2% and 8.8%, respectively. Recent use of analgesics or antipyretics and current cat ownership were associated with the risk of mild persistent AR. Sensitizations to *Dermatophagoides Pteronyssinus (Der p)*, Japanese hop and cat were associated with moderate to severe persistent AR. Children with moderate to severe AR had a higher risk of current asthma and BHR compared to mild AR cases (adjusted odds ratio [aOR], 5.26; 95% confidence interval [CI], 1.77–15.62). Moderate to severe AR with allergic sensitization was associated with the highest risk of BHR (aOR, 11.77; 95% CI, 3.40–40.74).
Conclusions: Moderate to severe-persistent AR is more closely related to respiratory comorbidities and sensitizations than mild AR. Stratifying the AR phenotype by ARIA classification may assist in disease management.

Keywords: Allergic rhinitis; classification; risk factor; child; phenotype; bronchial hyperreactivity; cohort study; prevalence

INTRODUCTION

Allergic rhinitis (AR) is not only a common chronic disease in children but is also a major global health problem that impacts on the quality of life of both the affected children and their caregivers.[1] The AR and its Impact on Asthma (ARIA) classification was introduced about 10 years ago and is continuously updated in different areas such as clinical symptoms, diagnostic procedures and treatment.[2-4] It has been used to optimize care and increase the ability of clinicians to control AR in pediatric patients. The prevalence of self-reported AR in children worldwide has been estimated at approximately 2% to 25%.[5] In Korea, the prevalence of AR in children had increased rapidly in a prior International Study of Asthma and Allergies in Children (ISAAC), and also in several general population studies.[6-8] In these previous studies, the prevalence of rhinitis symptoms in the prior 12 months in children aged 6–7 years was reported to be 31.0% in 1995,[6] 29.7% in 2000[6] and 43.6% in 2010.[8] However, few studies to date have investigated the prevalence of AR in children from a population-based birth cohort in accordance with the ARIA classifications.

Although AR is known to be linked with other allergic disorders, such as asthma and atopic dermatitis, there has been little investigation of the risk factors or comorbidities associated with AR according to the ARIA classification. Moreover, the studies that have been conducted lack data on the association between AR phenotype and either the sensitization to specific allergens or bronchial hyperresponsiveness (BHR).

We aimed in our current study to investigate the prevalence, risk factors and comorbidities, including allergen sensitization and BHR, related to AR in accordance with the ARIA classification in 7-year-old children from a general population-based birth cohort in Korea.

MATERIALS AND METHODS

Study participants

Study participants were enrolled from the Panel Study of Korean Children (PSKC) birth cohort that we previously established to provide nationwide longitudinal data on childhood development.[9,10] This cohort recruited 2,078 mother-baby dyads using 2-step stratified

random sampling across Korea in 2008 and has since followed these subjects annually. A total of 1,577 children were followed up in 2015. Of these subjects, 633 underwent laboratory tests for allergic diseases at the 16 participating regional hospitals in the cohort study (**Fig. 1**). These tests included skin prick tests, blood tests, standard spirometry and a bronchial provocation test with Provocholine (Provocholine®, Methapharm Inc., Ontario, Canada).

Doctors at each regional study hospital, mainly comprised of board-certified pediatric allergists, conducted laboratory screening of the PSKC cohort. Detailed histories and physical examinations of the cohort subjects were taken to verify the histories of asthma, AR, atopic dermatitis or other allergies and to record the differential diagnosis in each case. Physical examinations were conducted to evaluate past and present allergic diseases and AR was categorized according to the ARIA classification.

A flowchart for the subjects analyzed in our current study is shown in **Fig. 1**. Six hundred and thirty-three of these children visited a regional hospital, and complete information regarding AR history and ARIA classification was obtained in 606 of these cases. **Table 1** presents the characteristics of subjects who visited the regional study hospitals compared to the PSKC subjects who declined these visits. A past history of bronchiolitis was higher in the hospital-visiting subjects, but no other baseline characteristics were significantly different between the 2 groups.

The Institutional Review Board of Asan Medical Center reviewed and approved the current study protocol (IRB No. 2015-0907). Written consent was obtained from all parents and guardians following a detailed explanation of the study.

Skin prick test and bronchial provocation test

The skin prick test was conducted according to a standardized method.[11] A total of 18 allergens were tested in this way including histamine and saline as a positive and negative

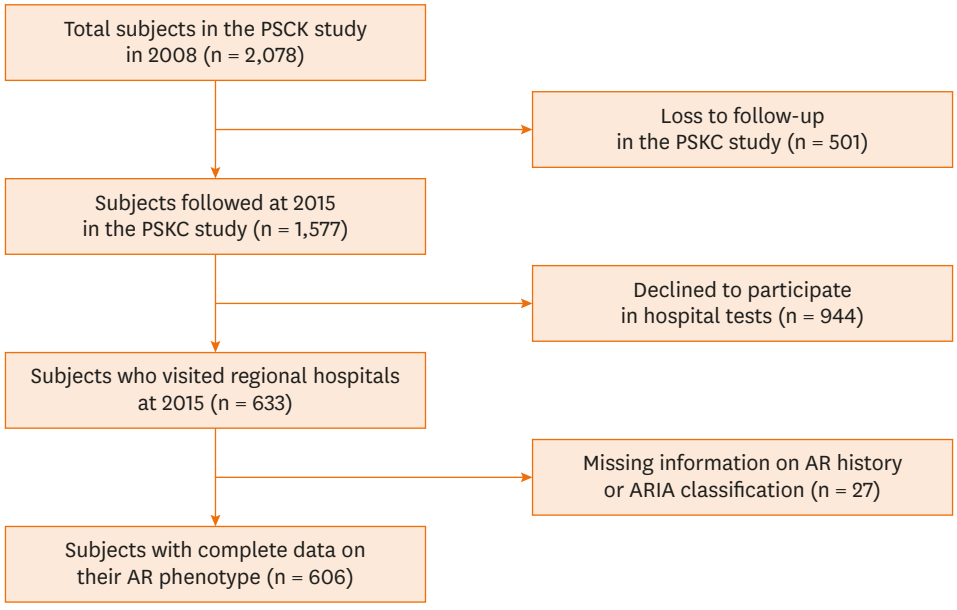

Fig. 1. Flow chart of the study subjects.
PSKC, Panel Study on Korean Children; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma.

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Table 1. Characteristics of the whole Panel Study of Korean Children

Characteristics	Visiting subjects No./total No. (%)* (n = 633)	Non-visiting subjects No./total No. (%)* (n = 944)	*P* value
Sex (male/female)	342/291	467/477	0.076
Parental history of allergic disease	196/607 (32.3)	309/881 (35.1)	0.265
Environmental tobacco smoking	234/633 (37.0)	380/944 (40.3)	0.189
Maternal education level			0.446
≤ High school	185 (29.3)	290 (30.8)	
College	412 (65.2)	605 (64.1)	
Graduate school	35 (5.5)	46 (4.9)	
Past history of bronchiolitis	154/632 (24.4)	172/939 (18.3)	0.004
Use of antibiotics in infancy	349/633 (55.1)	500/943 (53.0)	0.410
Current pet ownership	48/627 (7.7)	83/931 (8.9)	0.403

*Data are presented as a number (percentage) of patients unless otherwise indicated.

control, respectively. Inhalant and food allergens which are common in Korea were used as causative allergens (Allergopharma GmbH & Co. KG, Darmstadt, Germany), including 2 kinds of house dust mites (*Dermatophagoides pteronyssinus [Der p]* and *Dermatophagoides farinae [Der f]*), dog and cat epithelia, cockroaches, 2 fungal strains (*Alternaria alternate, Aspergillus fumigatus*), outdoor inhalation antigens such as pollen from grass, ragweed, mugwort, alder, oak, Japanese hop, birch and hazel and food allergens(egg whites, milk and peanut). When the positive control response exceeded 3 mm and the wheal size for the tested allergen was greater than the wheal size of the positive control, we defined the subject as being sensitized to this allergen. Drugs, such as antihistamines, which can affect skin prick tests were withdrawn completely for 2 weeks before the test.

The bronchial provocation test was conducted in accordance with the American Thoracic Society guidelines.[12] Briefly, fresh solutions of Provocholine were prepared in buffered saline solution at concentrations of 0.0625, 0.25, 1, 4 and 16 mg/mL. Subjects inhaled normal saline until the lung reached its maximum volume capacity and held their breath for approximately 5 seconds, which was repeated 5 times. We then measured the baseline FEV1 at 90 seconds from the fifth saline inhalation. Provocholine was then inhaled 5 times at each concentration and the FEV1 was measured again in the same manner which were repeated until either it showed a decrease of more than 20% compared to the baseline or the subjects reached the final Provocholine concentration of 16 mg/mL. The provocative concentration of Provocholine that caused a 20% decrease in the baseline FEV1 (PC_{20}) was thereby calculated. We defined a BHR to Provocholine as a PC_{20} < 8 mg/mL.

Definition of AR in accordance with the ARIA classification, current asthma, current eczema and allergic sensitization

The AR phenotype was classified by the hospital physicians in accordance with the ARIA classification in children who had ever been diagnosed with AR and had nasal symptoms within the previous 12 months that was unrelated to respiratory tract infections. AR duration was thereby classified as persistent (symptoms appearing more than 4 days per week and for more than 4 weeks) or intermittent (symptoms appearing for less than 4 days a week or for less than 4 weeks). AR severity was classified as mild or moderate/severe in accordance with the presence (moderate/severe) or absence (mild) of any of the following items: 1) sleep disturbance, 2) impairment of daily activities, leisure and/or sports, 3) impairment of school performance or 4) bothersome symptoms.[1] For statistical analysis, a control group was selected comprising the subjects in the cohort who visited a hospital but had never been diagnosed with AR.

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Current asthma was defined as both physician-diagnosed asthma-ever and a wheezy episode during the prior 12 months recorded during a pediatric allergist interview. Current eczema was defined as an episode during the previous 12 months. Risk factors for AR were analyzed using the responses to the 2015 questionnaires for the PSKC cohort. Allergic sensitization was defined as a sensitization to 1 or more allergens on a skin prick test.

Statistical analysis

Statistical analyses were conducted using SPSS version 23 (SPSS, Chicago, IL, USA). The χ^2 test was performed to compare subjects who visited a regional hospital or not. Logistic regression analyses were conducted to investigate risk factors affecting AR, and the odds ratio (OR) and 95% confidence interval (CI) values were calculated with adjustment for the following confounders: sex, maternal education levels, history of second-hand smoking, residential area and economic status. However, these factors did not include parental histories of allergic diseases which were ascertained by questionnaire.

RESULTS

Prevalence of the AR phenotype in 7-year-old Korean children according to the ARIA classification

The proportion of 7-year-old Korean children in our current study cohort who had ever been diagnosed with AR by a physician and developed nasal symptoms within the prior 12 months was 46.0% (**Fig. 2**). Mild-intermittent AR showed the highest prevalence in the study population at 29.5% with mild-persistent AR at 7.8%, moderate to severe-intermittent AR at 3.1%, and moderate to severe persistent AR at 5.6%.

Risk factors for AR according to the ARIA classification

The recent (prior 12 months) use of analgesics or antipyretics (adjusted OR [aOR], 2.32; 95% CI, 1.03–5.24) and current cat ownership (aOR, 10.18; 95% CI, 1.46–71.23) were found to be risk factors for mild persistent AR. Each one of the AR phenotypes was strongly associated

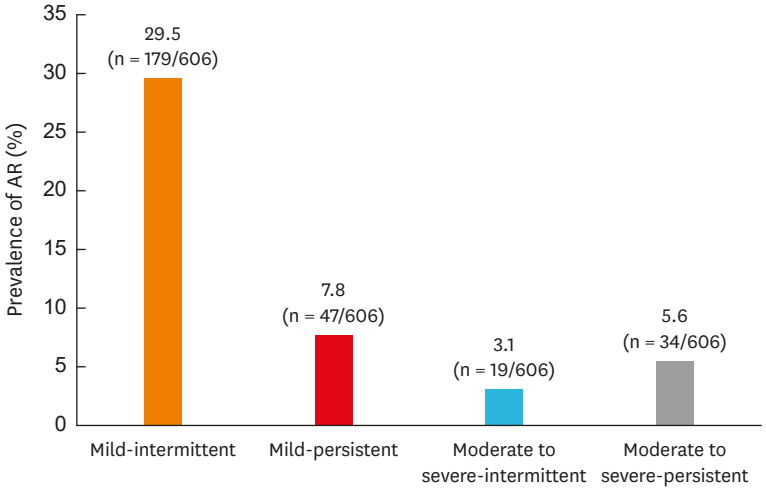

Fig. 2. Prevalence of AR in 7-year-old children according to their Allergic Rhinitis and its Impact on Asthma classification.
AR, allergic rhinitis.

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with a history of asthma diagnosis and a family history of allergic diseases, regardless of severity (**Table 2**).

Positive sensitizations on skin prick tests showing an association with the AR phenotype according to the ARIA classification

When AR was classified into 4 groups according to the ARIA classification, a moderate to severe persistent AR phenotype was found to be related to allergic sensitization (aOR, 2.40; 95% CI, 1.01–5.72), whereas mild-persistent AR showed an association with a sensitization to *Alternaria* (aOR, 6.81; 95% CI, 1.03–45.03). A sensitization to *Der p* (aOR, 2.75; 95% CI, 1.18–6.38), Japanese hop (which is a major cause of weed pollinosis in Korea) (aOR, 5.16; 95% CI, 1.51–17.59) and cat (aOR, 5.28; 95% CI, 1.17–23.63) increased the risk of moderate to severe persistent AR (**Table 3**).

When AR was classified into 2 groups according to its severity (mild versus moderate to severe), the moderate to severe AR phenotype was found to be related to sensitization to Japanese hop (aOR, 3.18; 95% CI, 1.10–9.15) and to cat (aOR, 8.87; 95% CI, 1.72–45.73) compared to the mild AR phenotype (**Supplementary Table S1**). When AR was stratified into 2 groups by persistence (intermittent versus persistent), persistent AR showed a relationship to sensitization to *Der p* (aOR, 3.18; 95% CI, 1.10–9.15) compared to intermittent AR (**Supplementary Table S2**).

Comorbidities according to the AR phenotype

Mild-intermittent AR increased the risk of current asthma (aOR, 18.48; 95% CI, 2.11–161.88), BHR (PC_{20} < 8 mg/mL) (aOR, 2.29; 95% CI, 1.27–4.14), and current eczema (aOR, 3.06; 95% CI, 1.45–6.45; **Table 4**). Mild-persistent AR increased the risk of current asthma (aOR, 16.63; 95% CI, 1.34–207.13), but not of BHR or current eczema. Moderate to severe-intermittent AR increased the risk of current asthma (aOR, 331.66; 95% CI, 27.26–4,035.98) and BHR (aOR, 4.45; 95% CI, 1.39–14.27), but did not correlate with current eczema. Moderate to severe-persistent AR also increased the risk of current asthma (aOR, 41.01; 95% CI, 3.62–464.15) and BHR (aOR, 3.91; 95% CI, 1.50–10.23), but not current eczema. Mild-persistent AR (aOR,

Table 2. Risk factors for AR according to the ARIA classification in 7-year-old Korean children

Risk odds of AR	aOR* (95% CI)			
Factors	Mild (n = 226)		Moderate to severe (n = 53)	
	Intermittent (n = 179)	Persistent (n = 47)	Intermittent (n = 19)	Persistent (n = 34)
Exposure variables				
History of bronchiolitis before 3 years of age	1.48 (0.92–2.37)	1.17 (0.55–2.51)	1.70 (0.58–5.00)	1.88 (0.80–4.42)
Recent use of analgesics or anti-pyretics (within 12 mon)	1.02 (0.67–1.55)	2.32‡ (1.03–5.24)	1.85 (0.54–6.34)	1.19 (0.53–2.70)
Frequent use of antibiotics in infancy (≥ 3 days and ≥ 3 times)	1.14 (0.68–1.92)	1.10 (0.42–2.85)	1.38 (0.36–5.26)	1.89 (0.76–4.71)
Current dog ownership (within 12 mon)	1.23 (0.56–2.70)	1.20 (0.24–6.00)	2.76 (0.28–27.72)	-
Current cat ownership (within 12 mon)	1.21 (0.25–5.82)	10.18‡ (1.46–71.23)	-	2.48 (0.24–26.00)
History of recent remodeling (within 12 mon)	0.82 (0.47–1.43)	1.36 (0.59–3.17)	1.72 (0.47–6.33)	0.55 (0.16–1.96)
Current indoor mold exposure	1.16 (0.77–1.76)	1.37 (0.68–2.74)	0.98 (0.35–2.77)	1.42 (0.64–3.17)
Health outcomes				
Past history of asthma diagnosis	3.41‡ (1.30–8.93)	2.13 (0.56–8.20)	9.75‡ (1.53–61.91)	9.06§ (2.64–31.08)
Past history of FA diagnosis	1.83 (0.83–4.04)	1.05 (0.26–4.16)	-	1.92 (0.50–7.37)
Past history of AD diagnosis	1.67‡ (1.05–2.65)	0.97 (0.43–2.17)	0.19 (0.03–1.01)	2.20 (0.95–5.09)
Paternal allergic disease	1.91†,§ (1.25–2.90)	4.01†,§ (1.96–8.17)	5.98†,§ (1.79–20.00)	1.07† (0.45–2.55)
Maternal allergic disease	2.89†,§ (1.90–4.40)	3.58†,§ (1.80–7.15)	4.55†,‡ (1.40–14.81)	2.06† (0.91–4.66)

Control group for AR: All subjects who have never been diagnosed with AR by a physician.
AD, atopic dermatitis; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; FA, food allergy; CI, confidence intervals; aOR, adjusted odds ratio.
*Adjusted by sex, maternal education levels, parental history of allergic diseases, history of second-hand smoking, residential area, and economic status; †Adjusted by sex, maternal education levels, history of second-hand smoking, residential area, and economic status, but excluding parental history of allergic diseases; ‡P < 0.05; §P < 0.01.

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Table 3. Association of positive sensitization on skin prick tests with AR according to the ARIA classification

Positive sensitization on skin prick test	aOR* (95% CI)			
	Mild (n = 226)		Moderate to severe (n = 53)	
	Intermittent (n = 179)	Persistent (n = 47)	Intermittent (n = 19)	Persistent (n = 34)
SPT any positive (n = 259)	1.38 (0.90–2.12)	1.44 (0.68–3.01)	1.18 (0.35–4.00)	2.40† (1.01–5.72)
Der f (n = 204)	1.15 (0.75–1.78)	1.40 (0.67–2.92)	1.04 (0.35–3.07)	1.43 (0.62–3.28)
Der p (n = 225)	1.32 (0.86–2.02)	1.54 (0.75–3.16)	1.44 (0.48–4.28)	2.75† (1.18–6.38)
Alternaria (n = 13)	1.13 (0.25–5.09)	6.81† (1.03–45.03)	-	2.62 (0.23–29.94)
Aspergillus (n = 6)	0.64 (0.08–5.23)	5.98 (0.34–104.00)	12.75 (0.47–347.46)	-
Grasses (n = 21)	1.71 (0.57–5.08)	1.80 (0.32–10.07)	1.50 (0.16–14.49)	2.57 (0.46–14.53)
Alder (n = 18)	2.28 (0.73–7.11)	0.58 (0.06–5.69)	-	1.12 (0.12–10.79)
Birch (n = 26)	1.80 (0.69–4.73)	1.24 (0.23–6.79)	4.50 (0.75–26.90)	0.85 (0.09–7.75)
Oak (n = 18)	1.44 (0.43–4.79)	0.65 (0.07–6.03)	1.32 (0.12–14.44)	3.18 (0.55–18.18)
Japanese heopshop (n = 40)	1.64 (0.69–3.89)	1.25 (0.24–6.52)	10.20‡ (1.78–58.43)	5.16‡ (1.51–17.59)
Mugwort (n = 18)	1.71 (0.51–5.71)	2.11 (0.33–13.58)	1.92 (0.19–19.42)	4.08 (0.68–24.47)
Ragweed (n = 6)	1.12 (0.15–8.53)	-	3.24 (0.24–44.06)	-
Hazel (n = 23)	0.90 (0.31–2.62)	1.66 (0.39–7.04)	1.23 (0.14–11.19)	0.65 (0.08–5.62)
Peanut (n = 2)	1.70 (0.08–35.53)	-	-	-
Egg white (n = 3)	6.65 (0.52–85.11)	-	-	-
Dog (n = 24)	0.84 (0.30–2.32)	2.92 (0.75–11.42)	1.61 (0.11–24.75)	0.84 (0.09–7.59)
Cat (n = 18)	0.39 (0.09–1.58)	0.47 (0.05–4.36)	4.55 (0.38–55.12)	5.28† (1.17–23.63)
Cockroach (n = 2)	2.47 (0.13–47.32)	-	-	-

Control group for AR: among subjects who visited hospital, the subjects who have never been diagnosed with AR by physician.
AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; aOR, adjusted odds ratio; CI, confidence interval; SPT, skin prick test.
*Adjusted by sex, maternal education levels, parental history of allergic diseases, history of second-hand smoking, residential area, and economic status; †$P < 0.05$; ‡$P < 0.01$.

Table 4. Comorbidities according to AR classifications

Comorbidities of AR	aOR* (95% CI)							
	Mild				Moderate to severe			
	Intermittent		Persistent		Intermittent		Persistent	
	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)
Current asthma	7/177 (3.9)	18.48† (2.11–161.88)	2/46 (4.3)	16.63‡ (1.34–207.13)	6/19 (31.6)	331.66† (27.26–4,035.98)	3/34 (8.8)	41.01† (3.62–464.15)
PC_{20} < 8 mg/mL	31/152 (20.4)	2.29† (1.27–4.14)	6/46 (13.0)	0.92 (0.32–2.65)	6/17 (35.3)	4.45‡ (1.39–14.27)	9/31 (29.0)	3.91† (1.50–10.23)
BHR without current asthma	28/149 (18.8)	2.18‡ (1.18–4.02)	5/45 (11.1)	0.99 (0.34–2.84)	2/13 (15.4)	1.48 (0.29–7.53)	8/30 (26.7)	3.54‡ (1.30–9.67)
Current eczema	42/92 (45.7)	3.06‡ (1.45–6.45)	6/15 (40.0)	1.00 (0.25–3.92)	4/10 (40.0)	2.14 (0.49–9.45)	7/16 (43.8)	2.54 (0.69–9.33)
Allergic sensitization	76/168 (45.2)	1.46 (0.94–2.25)	25/45 (55.6)	2.08† (1.01–4.27)	8/15 (53.3)	1.65 (0.55–4.99)	21/32 (65.6)	2.58† (1.12–5.94)

Control group for AR: all subjects who have never been diagnosed with AR by a physician.
AR, allergic rhinitis; aOR, adjusted odds ratio; CI, confidence interval; BHR, bronchial hyperresponsiveness.
*Adjusted by sex, maternal education levels, parental history of allergic diseases, history of second-hand smoking, residential area, and economic status; †$P < 0.05$; ‡$P < 0.01$.

2.08; 95% CI, 1.01–4.27) and moderate to severe-persistent AR (aOR, 2.58; 95% CI, 1.12–5.94) increased the risk of allergic sensitization. Comparing the risk of BHR in accordance with the AR phenotype, we found that moderate to severe AR had a higher OR than mild-intermittent AR (**Table 4** and **Fig. 3**).

When AR was classified according to symptom severity, children with moderate to severe AR showed a higher risk of current asthma (aOR, 5.26; 95% CI, 1.77–15.62) and BHR (aOR, 2.32; 95% CI, 1.01–5.32). Notably however, children with persistent AR did not have a higher risk of current asthma or BHR than those with intermittent AR. There was also no statistical difference found in the prevalence of current eczema according to the AR phenotype stratified using the ARIA classification (**Table 5**).

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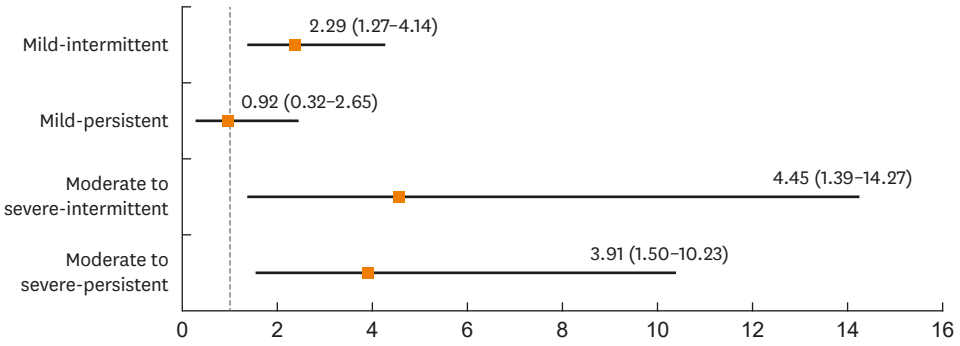

Fig. 3. Adjusted odds ratio and 95% confidence intervals for the risk of bronchial hyperresponsiveness according to the AR phenotype by Allergic Rhinitis and its Impact on Asthma classification.
AR, allergic rhinitis.

Table 5. Comorbidities according to AR classifications: comparison between mild, moderate to severe, intermittent and persistent AR

Comorbidities of AR	Mild vs. moderate to severe				Intermittent vs. persistent			
	Mild		Moderate to severe		Intermittent		Persistent	
	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)
Current asthma	9/223 (4.0)	1 (reference)	9/53 (17.0)	5.26‡ (1.77–15.62)	13/196 (6.6)	1 (reference)	5/80 (6.2)	0.70 (0.22–2.19)
PC_{20} < 8 mg/mL	37/198 (18.7)	1 (reference)	15/48 (31.3)	2.32† (1.01–5.32)	37/169 (21.9)	1 (reference)	15/77 (19.5)	0.80 (0.37–1.72)
BHR without current asthma	33/194 (17.0)	1 (reference)	10/43 (23.3)	1.64 (0.65–4.15)	30/162 (18.5)	1 (reference)	13/75 (17.3)	0.93 (0.42–2.07)
Current eczema	48/107 (44.9)	1 (reference)	11/26 (42.3)	1.37 (0.42–4.46)	46/102 (45.1)	1 (reference)	13/31 (41.9)	0.81 (0.27–2.44)
Allergic sensitization	101/213 (47.4)	1 (reference)	29/47 (61.7)	1.59 (0.77–3.28)	84/183 (45.9)	1 (reference)	31/46 (59.7)	1.83 (0.98–3.42)

AR, allergic rhinitis; aOR, adjusted odds ratio; CI, confidence interval; BHR, bronchial hyperresponsiveness.
*Adjusted by sex, maternal education levels, parental history of allergic diseases, history of second-hand smoking, residential area, and economic status; †P < 0.05; ‡P < 0.01.

Table 6. Comorbidities according to AR classifications: comparison between mild and moderate to severe AR, depending on allergic sensitization

Comorbidities of AR	Mild				Moderate to severe			
	Allergic sensitization (–)		Allergic sensitization (+)		Allergic sensitization (–)		Allergic sensitization (+)	
	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)	No./total No. (%)	aOR* (95% CI)
Current asthma	3/111 (2.7)	1 (reference)	5/99 (5.1)	1.51 (0.31–7.47)	4/18 (22.2)	8.68† (1.51–50.01)	4/29 (13.8)	6.61† (1.16–37.6)
PC_{20} < 8 mg/mL	8/101 (7.9)	1 (reference)	28/86 (32.6)	6.01‡ (2.29–15.75)	2/17 (11.8)	2.01 (0.33–12.32)	11/26 (42.3)	11.77‡ (3.40–40.74)
BHR without current asthma	7/100 (7.0)	1 (reference)	25/83 (30.1)	5.29‡ (1.99–14.04)	0/15 (0.0)	-	9/24 (37.5)	9.27‡ (2.54–33.76)
Current eczema	18/43 (41.9)	1 (reference)	25/51 (49.0)	2.04 (0.68–6.14)	4/8 (50.0)	1.39 (0.22–8.82)	5/13 (38.5)	1.39 (0.24–8.23)

AR, allergic rhinitis; aOR, adjusted odds ratio; CI, confidence interval; BHR, bronchial hyperresponsiveness.
*Adjusted by sex, maternal education levels, parental history of allergic diseases, history of second-hand smoking, residential area, and economic status; †P < 0.05; ‡P < 0.01.

The results presented in **Table 6** indicate that BHR is more related to AR with allergic sensitization than to mild AR without allergic sensitization, and that among each phenotype, a moderate to severe AR phenotype with allergic sensitization assessed by skin prick tests is associated with the highest risk of BHR (aOR, 11.77; 95% CI, 3.40–40.74) compared to a mild AR phenotype without allergic sensitization.

DISCUSSION

We calculated the prevalence of AR phenotypes according to the ARIA classification in 7-year-old Korean children enrolled from a nationwide population-based birth cohort study. In addition, we identified that the associated factors and allergen sensitization profiles for current AR in children at age 7 years differ in the AR phenotype determined using the ARIA

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classification. Children with a moderate to severe-persistent AR phenotype showed a higher risk of current asthma and BHR compared to those with a mild AR phenotype, and these findings were more prominent in cases of moderate to severe AR with allergic sensitization.

There have been several previous studies on AR based on the ARIA classification in children. However, few prior studies have been conducted on AR risk factors and comorbidities with asthma or BHR in accordance with disease severity in a general population-based epidemiologic cohort. Our current findings suggest that the severity of AR symptoms by ARIA classification may better reflect the AR phenotype and is more closely related to respiratory comorbidities than the persistence of AR in early schoolchildren. These observations thus provide useful new insights into the AR phenotype in a real clinical setting.

The prevalence of allergic diseases in Korea was first investigated in 1995[6] following the findings of ISAAC studies that proposed a uniform approach to prevalence surveys through standardized questionnaires.[13] Subsequent national epidemiological surveys in Korea were then conducted in 2000 and 2010.[6,8] The findings of the 2 surveys indicated a prevalence of rhinitis symptoms in elementary school students in the prior 12 months of 31.0% in 1995 and 29.7% in 2000.[6] In 2010, however, the prevalence rate of allergic diseases in primary elementary school students at age 6–7 years and in first year middle school students at age 12–13 years were 43.6% and 42.6%, respectively. In our study, the current AR incidence in 7-year-old children, defined as physician-diagnosed AR plus associated symptoms within the previous 12 months, was measured at 46.0% and the prevalence of AR symptoms in the prior 12 months at 63.4% (384/606). Our finding that the prevalence of AR has gradually increased in Korea is consistent with the trend described in previous domestic studies.[6,8]

The increased incidences of allergic diseases in Korea are presumed to be due to lifestyle and environmental changes.[7,14] Allergic diseases, such as AR, are known to be caused by genetic disposition and environmental factors. Through several previous twin studies, a genetic background in terms of a family history of allergic disease has been shown to be the strongest risk factor for the development of allergy symptoms.[15] Environmental factors,[16,17] nutrient intake,[18,19] hygiene standards,[20,21] maternal stress[22,23] and ownership of pets[22] have also been implicated in the development of allergic disease. In our study cohort, current AR was found to be strongly associated with history of asthma diagnosis and family history of allergic diseases as reported in other previous studies.[15] We also compared risk factors for AR phenotypes by the ARIA classification in a general population-based context. Our findings indicate that the recent use of analgesics or antipyretics and current cat ownership are associated with the risk of mild persistent AR.

The aeroallergens that affect AR symptoms may vary according to geographical regions and particular seasons. A prior domestic study concluded that seasonal pollens do not play a role in the seasonal prevalence of AR in terms of the severity of symptoms.[24] However, in our study, both house dust mites and Japanese hop were found to be significant allergens in moderate to severe persistent AR in Korean children. In addition, a moderate to severe AR phenotype in our current analysis was found to be related to sensitization to Japanese hop and cat as compared to a mild AR phenotype. Moreover, the moderate to severe-persistent AR phenotype showed the strongest association with allergen sensitization as assessed by skin prick testing. We further found that a mild AR phenotype with a history of asthma was related to *Der p* sensitization compared to a mild AR phenotype without asthma history. An

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intermittent AR phenotype with a history of asthma was found to be related to sensitization to cat compared to an intermittent AR phenotype without a history of asthma.

Rhinitis is a disorder that has always been considered in conjunction with other allergic counterparts such as asthma and eczema. In our study series, we investigated AR comorbidities in children in accordance with their ARIA classification. The children with moderate to severe AR had a higher risk of current asthma, but not current eczema compared to those with mild AR. AR and asthma are considered to be a single airway disease and their relationship has been investigated in several studies in accordance with the AR phenotype. In a prior multi-center cross-sectional study, asthma prevalence was reported not to correlate with the ARIA classification of rhinitis in adults.[25] Another previous cross-sectional study revealed that asthma prevalence increases with the duration and severity of rhinitis in adults.[26] Few studies, however, have investigated the relationship between asthma and AR in children according to the ARIA classification. In a previous Portuguese nationwide and population-based study, current wheezing showed a strong association with moderate to severe-persistent AR in preschool children.[27] Another prospective study on children aged 6–12 years reported that the severity and duration of AR were significantly associated with asthma,[28] which is comparable to our findings.

It is now clear from the results of a large number of previous cross-sectional studies that AR is strongly associated with not only asthma but also BHR. The prevalence of BHR has been reported to be higher in non-asthmatic patients with AR than in normal subjects.[29-31] In a population-based longitudinal study,[30] 9.7% of adult patients with AR and no BHR developed this condition after 9 years. In addition, BHR symptoms have been shown to improve after AR treatment.[32] These findings suggest that AR may contribute to lower airway inflammation[33] via the nasobronchial reflex, mouth breathing and postnasal drip.[30] In our study, children with moderate to severe AR had a higher risk of BHR compared to children with mild AR, which is consistent with the finding of a previous study.[34] Importantly, we further showed that the severity of AR symptoms are a more important factor for the onset of respiratory comorbidities than the persistence of symptoms in early school children, particularly in cases with allergic sensitization. These findings differ from those of previous studies that have reported a relationship between persistent AR symptoms and BHR.[29,35,36] Several prior case control studies[29,36] in non-asthmatic children have also indicated that the persistence of AR symptoms is significantly associated with BHR, and a another prospective cohort study[35] of rhinitis children only aged 6–15 years reported that the persistence but not severity of rhinitis was a significant predictor of BHR. In our study, the number of subjects with a persistent phenotype was not so many because our study is a general population-based study. Especially, the number of subjects in persistent phenotypes (n=81: subjects; mild-persistent AR, 47; subjects with moderate to severe persistent AR, 34) was smaller than those of intermittent phenotypes (n=198: subjects; mild-intermittent AR, 179, subjects with moderate to severe-intermittent AR, 19). The statistical significance may be affected by the low number of subjects. Therefore, it needs a larger general population study in the future. The persistence of AR may be misinterpreted by recurrent respiratory infections and sinusitis symptoms. However, there have been few previous general population-based studies, on the relationship between BHR and AR phenotype in children in accordance with the ARIA classification as in our report. Our analyses show that there is a relationship between AR severity and BHR in 7-year-old children from the general Korean population, which includes most children with mild AR symptoms.

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The greatest strength of our present study was that all of the subjects were enrolled from a population-based nationwide birth cohort study that visited their regional hospital and received a physical examination from an allergy specialist, in addition to an allergic examination and bronchial challenge test. Pediatric allergy specialists thus verified the AR phenotypes using the ARIA classification and thus raised the diagnostic accuracy of this condition by directly taking a detailed history and conducting a physical examination for all of the subjects. However, there were also several limitations of our present study of note. In the first instance, it was possible that our PSKC birth cohort subjects who attended their regional hospital had more pronounced medical conditions than the subjects who declined to do so, and the prevalence of AR was significantly higher in the hospital visiting group than in the non-hospital visiting group in the questionnaire assessment (**Table 1** and **Supplementary Table S3**). Even though we used AR definitions by 'Pediatric allergist interview' to improve the accuracy of AR diagnosis, this may have led to an overestimation of the prevalence of moderate to severe AR in the general population. Additionally, the effects of upper respiratory infection and sinusitis may be misinterpreted as persistent symptoms of rhinitis in this age group of children. In addition, the data we collected on risk factors were largely dependent on the recall of the parents and caregivers, which could not be verified by the treating physician. We used the ISAAC questionnaire to evaluate the presence of allergic diseases, which is widely used and has previously been validated in a large epidemiologic study.[13] We also assumed that the pediatric allergy specialist interviews would have compensated for some of the limitations of the ISAAC questionnaire.

We conclude from our findings that the moderate to severe-persistent AR phenotype is more closely related to respiratory comorbidities and allergen sensitization than the mild AR phenotype. In addition, a novel finding from our analysis is that the severity of AR is more closely related to current asthma and BHR than its persistence in young children. The results of our study will help physicians identify rhinitis phenotypes that require specific treatments and prevent asthma and BHR development.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Association of AR with positive sensitization on a skin prick test according to the Allergic Rhinitis and its Impact on Asthma classification of mild versus moderate to severe AR

Click here to view

Supplementary Table 2

Association of AR with positive sensitization on a skin prick test according to the Allergic Rhinitis and its Impact on Asthma classification of intermittent versus persistent AR

Click here to view

Supplementary Table 3

Prevalence of AR in 7-year-old children from the Panel Study on Korean Children study

Click here to view

REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
PUBMED | CROSSREF
2. Bousquet J, Schünemann HJ, Zuberbier T, Bachert C, Baena-Cagnani CE, Bousquet PJ, et al. Development and implementation of guidelines in allergic rhinitis – an ARIA-GA2LEN paper. Allergy 2010;65:1212-21.
PUBMED | CROSSREF
3. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy 2012;67:18-24.
PUBMED | CROSSREF
4. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017;140:950-8.
PUBMED | CROSSREF
5. Katelaris CH, Lee BW, Potter PC, Maspero JF, Cingi C, Lopatin A, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. Clin Exp Allergy 2012;42:186-207.
PUBMED | CROSSREF
6. Hong SJ, Ahn KM, Lee SY, Kim KE. The prevalences of asthma and allergic diseases in Korean children. Korean J Pediatr 2008;51:343-50.
CROSSREF
7. Kim WK, Kwon JW, Seo JH, Kim HY, Yu J, Kim BJ, et al. Interaction between IL13 genotype and environmental factors in the risk for allergic rhinitis in Korean children. J Allergy Clin Immunol 2012;130:421-426.e5.
PUBMED | CROSSREF
8. Lee Y, Choi J, Park MR, Kim J, Kim WK, Park YM, et al. Analysis of regional prevalence of allergic diseases in Korean school children. Allergy Asthma Respir Dis 2015;3:62-9.
CROSSREF
9. Bahk J, Yun SC, Kim YM, Khang YH. Impact of unintended pregnancy on maternal mental health: a causal analysis using follow up data of the Panel Study on Korean Children (PSKC). BMC Pregnancy Childbirth 2015;15:85.
PUBMED | CROSSREF
10. Jung S, Suh DI, Lee SY, Yoon J, Cho HJ, Kim YH, et al. Prevalence, risk factors and cutoff values for bronchial hyperresponsiveness to provocholine in 7-year-old children. Allergy Asthma Immunol Res 2018;10:466-77.
PUBMED | CROSSREF
11. Pepys J. Skin tests for immediate, type I, allergic reactions. Proc R Soc Med 1972;65:271-2.
PUBMED | CROSSREF
12. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000;161:309-29.
PUBMED
13. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998;351:1225-32.
PUBMED | CROSSREF

14. Lee SY, Kwon JW, Seo JH, Song YH, Kim BJ, Yu J, et al. Prevalence of atopy and allergic diseases in Korean children: associations with a farming environment and rural lifestyle. Int Arch Allergy Immunol 2012;158:168-74.
PUBMED | CROSSREF
15. van Beijsterveldt CE, Boomsma DI. Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. Eur Respir J 2007;29:516-21.
PUBMED | CROSSREF
16. Illi S, Weber J, Zutavern A, Genuneit J, Schierl R, Strunz-Lehner C, et al. Perinatal influences on the development of asthma and atopy in childhood. Ann Allergy Asthma Immunol 2014;112:132-139.e1.
PUBMED | CROSSREF
17. Thomson JA, Widjaja C, Darmaputra AA, Lowe A, Matheson MC, Bennett CM, et al. Early childhood infections and immunisation and the development of allergic disease in particular asthma in a high-risk cohort: a prospective study of allergy-prone children from birth to six years. Pediatr Allergy Immunol 2010;21:1076-85.
PUBMED | CROSSREF
18. Nwaru BI, Takkinen HM, Kaila M, Erkkola M, Ahonen S, Pekkanen J, et al. Food diversity in infancy and the risk of childhood asthma and allergies. J Allergy Clin Immunol 2014;133:1084-91.
PUBMED | CROSSREF
19. Magnusson J, Kull I, Rosenlund H, Håkansson N, Wolk A, Melén E, et al. Fish consumption in infancy and development of allergic disease up to age 12 y. Am J Clin Nutr 2013;97:1324-30.
PUBMED | CROSSREF
20. Strachan DP, Aït-Khaled N, Foliaki S, Mallol J, Odhiambo J, Pearce N, et al. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. Clin Exp Allergy 2015;45:126-36.
PUBMED | CROSSREF
21. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55 Suppl 1:S2-10.
PUBMED | CROSSREF
22. Park YB, Mo EK, Lee JY, Kim JH, Kim CH, Hyun IG, et al. Association between pet ownership and the sensitization to pet allergens in adults with various allergic diseases. Allergy Asthma Immunol Res 2013;5:295-300.
PUBMED | CROSSREF
23. Kozyrskyj AL, Mai XM, McGrath P, Hayglass KT, Becker AB, Macneil B. Continued exposure to maternal distress in early life is associated with an increased risk of childhood asthma. Am J Respir Crit Care Med 2008;177:142-7.
PUBMED | CROSSREF
24. Chung YJ, Cho IK, Lee KI, Bae SH, Lee JW, Chung PS, et al. Seasonal specificity of seasonal allergens and validation of the ARIA classification in Korea. Allergy Asthma Immunol Res 2013;5:75-80.
PUBMED | CROSSREF
25. Antonicelli L, Micucci C, Voltolini S, Feliziani V, Senna GE, Di Blasi P, et al. Allergic rhinitis and asthma comorbidity: ARIA classification of rhinitis does not correlate with the prevalence of asthma. Clin Exp Allergy 2007;37:954-60.
PUBMED | CROSSREF
26. Bousquet J, Annesi-Maesano I, Carat F, Léger D, Rugina M, Pribil C, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy 2005;35:728-32.
PUBMED | CROSSREF
27. Pereira AM, Morais-Almeida M, Santos N, Nunes C, Bousquet J, Fonseca JA. Severity of rhinitis and wheezing is strongly associated in preschoolers: a population-based study. Pediatr Allergy Immunol 2015;26:618-27.
PUBMED | CROSSREF
28. Di Cara G, Carelli A, Latini A, Panfili E, Bizzarri I, Ciprandi G, et al. Severity of allergic rhinitis and asthma development in children. World Allergy Organ J 2015;8:13.
PUBMED | CROSSREF
29. Cuttitta G, Cibella F, La Grutta S, Hopps MR, Bucchieri S, Passalacqua G, et al. Non-specific bronchial hyper-responsiveness in children with allergic rhinitis: relationship with the atopic status. Pediatr Allergy Immunol 2003;14:458-63.
PUBMED | CROSSREF
30. Shaaban R, Zureik M, Soussan D, Antó JM, Heinrich J, Janson C, et al. Allergic rhinitis and onset of bronchial hyperresponsiveness: a population-based study. Am J Respir Crit Care Med 2007;176:659-66.
PUBMED | CROSSREF

31. Ciprandi G, Cirillo I, Klersy C. Lower airways may also be affected in asymptomatic patients with recent onset of allergic rhinitis. Laryngoscope 2010;120:1288-91.
PUBMED | CROSSREF

32. Olivieri M, Mohaddes Zadeh MR, Talamini G, Lampronti G, Lo Cascio V. Local nasal immunotherapy and bronchial hyperreactivity in seasonal allergic rhinitis: an observational pilot study. J Investig Allergol Clin Immunol 2000;10:300-4.
PUBMED

33. Corren J. The impact of allergic rhinitis on bronchial asthma. J Allergy Clin Immunol 1998;101:S352-6.
PUBMED | CROSSREF

34. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108:S147-334.
PUBMED | CROSSREF

35. Kim SW, Han DH, Lee SJ, Lee CH, Rhee CS. Bronchial hyperresponsiveness in pediatric rhinitis patients: the difference between allergic and nonallergic rhinitis. Am J Rhinol Allergy 2013;27:e63-8.
PUBMED | CROSSREF

36. Choi SH, Yoo Y, Yu J, Rhee CS, Min YG, Koh YY. Bronchial hyperresponsiveness in young children with allergic rhinitis and its risk factors. Allergy 2007;62:1051-6.
PUBMED | CROSSREF