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Original article

Allergic sensitization to indoor and outdoor allergens and relevance to bronchial hyperresponsiveness in younger and older subjects

Background: Most previous epidemiological studies on the relationship between allergy and bronchial hyperresponsiveness (BHR) have made no distinction between sensitization to indoor and outdoor allergens. We studied the relationship between specific sensitization to allergen and BHR and further assessed whether this was different in young adults and older subjects.
Methods: Specific IgE to indoor allergens (house dust mite and cat) and outdoor allergens (timothy grass and birch) were measured using the CAP System. BHR was defined as $PD_{20} \leq 2$ mg methacholine. Multiple logistic regression analysis was performed to study independent relationships between BHR and specific IgE to indoor and outdoor allergens in 1018 young adults (20–44 years) and 909 older subjects (45–70 years).
Results: In the older age group specific IgE to indoor allergens was associated with BHR at a lower level (class 2) than in young adults (class ≥ 3). Young adults with multiple sensitization had the highest risk of BHR. Subjects who were exclusively sensitized to pollen did not show increased BHR in both age groups. Total IgE had, independently of sensitization, only a significant dose–response relationship with BHR in the oldest age group.
Conclusions: The association between sensitization and BHR is dependent on the nature of the allergen and the level of specific IgE. Furthermore, this study shows for the first time that total IgE is associated with BHR at older ages, independently of sensitization.

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Key words: age, bronchial hyperresponsiveness, indoor allergens, pollen, sensitization, total IgE.

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Both sensitization to allergens and bronchial hyperresponsiveness (BHR) are core characteristics of asthma. Sensitization to indoor allergens, i.e. house dust mite and cat, as well as sensitization to outdoor allergens, i.e. pollen, are frequently present either alone or in combination. Whereas it is clear in clinical practice that allergic sensitization may affect BHR, it is not fully clear whether sensitization to indoor and outdoor allergens are differently associated with BHR. So far, studies assessing associations between allergy and BHR defined allergy as the presence of one or more positive skin tests to common inhalant allergens (1–8) and only a few studies investigated allergy to specific allergens (9–12). This may have consequences for the association between allergy and BHR, since differences in physicochemical properties of allergens may result in different associations, assuming that contact of allergens to the mucosa of the lower airways plays a causal role in the development of BHR. If this assumption is correct, allergy to pollen may not be associated with BHR, since the particle size of pollen has been considered too large to penetrate the lower airways. Alternatively, indoor and outdoor allergens may interact differently with airway epithelial cells and some allergens may have greater potential for inducing allergic inflammation than others. However, allergy may also constitute an epiphenomenon of BHR, and if so, the nature of the allergen and the degree of sensitization are of less importance.

The prevalence of BHR has been shown to increase with more extensive allergy in children and young adults (1, 13–15), yet studies in older subjects are lacking. However, BHR is also frequently found in older subjects. The association between allergy and BHR may be less strong among older subjects compared to young adults, since the prevalence of sensitization to common inhalant allergens, in contrast to BHR, is lower at an older age (16). Besides, other risk factors, like the history of cigarette smoking and occupational exposure, probably become more important in the development of BHR at an older age (2).

Finally, serum total IgE has been shown to be closely related to BHR in children (17, 18). Yet, in adults this has scarcely been studied (11, 19).

We studied the independent association between sensitization to indoor and outdoor allergens and bronchial hyperresponsiveness using data collected during the European Community Respiratory Health Survey (20) among adults 20–70 years in the Netherlands. We also studied the independent association of total IgE with BHR in both age groups.

Material and methods

Subjects

The subjects studied were from a random sample of 4522 adults aged 20–70 years from the general population of three areas in the Netherlands studied between February 1992 and February 1993. The sample was stratified by gender and 10-year age groups. Complete data on questionnaire, lung function testing, measurement of bronchial responsiveness by methacholine provocation, and venous blood collection for IgE were obtained from 1927 subjects.

Measurements

All measurements were performed according to the protocols of the European Community Respiratory Health Survey (ECRHS) (20).

Total and specific IgE were measured using the Pharmacia CAP System. The CAP was performed in the laboratories of Pharmacia diagnostics AB, Uppsala. The assay was calibrated against the WHO Standard for IgE, with a range of 0.35–100 kU/l for specific IgE and 2–2000 kU/l for total IgE. Specific IgE was measured to the "indoor allergens" house dust mite (*Dermatophagoides pteronyssinus*) and cat, and the "outdoor allergens" timothy grass and birch. A specific IgE level of 0.35–0.70 kU/l was defined as class 1, 0.70–3.5 kU/l as class 2, and > 3.5 kU/l as class ≥ 3.

A high total IgE was defined as a total IgE value in the highest quartile of the population under study. Since total IgE is substantially higher in men than in women, these quartiles were calculated for both sexes separately: highest quartile > 68 kU/for women and > 105 kU/l for men.

Bronchial responsiveness was measured by methacholine chloride inhalation using a Mefar dosimeter. Subjects were advised to avoid smoking for 1 h, using a β_2-agonist or anticholinergic inhaler for 4 h or oral medication (β_2-agonist, theophylline or antimuscarinic) for 8 h before the test. In symptomatic subjects methacholine challenge was performed according to a long protocol of doubling the cumulative dose of methacholine after a starting dose of 7.8 μg up to a cumulative dose of 2 mg. In asymptomatic subjects a short protocol was followed in which doses were quadrupled after a starting dose of 15.6 μg. The challenge was stopped if there was a 20% fall in FEV_1 from the control value in the best of two technically satisfactory manoeuvres performed after each inhalation. Subjects who had a decline in FEV_1 of 20% or more after 2 mg or less methacholine were classified as bronchial hyperresponsive. Subjects who were not able to perform successful FEV_1 and FVC manoeuvres or had an FEV_1 less than 70% of the mean predicted value or an FEV_1 less than 1.5l were excluded from methacholine challenge. Other exclusion criteria were a heart attack in the last 3 months, any heart disease for which medication was used, epilepsy for which medication was used, pregnancy, breast-feeding or the use of a beta-blocker.

Statistical analyses

Prevalences of BHR by different classes of specific IgE to the four inhalant allergens were shown univariately and statistically tested with chi-squared tests. The independent effects of specific IgE to four different inhalant allergens on BHR were studied by multiple logistic regression analysis. The three classes of specific IgE were included as a categorical variable with those without specific IgE as a reference group. Total IgE and age were included as restricted cubic spline functions, and Wald statistics were performed to test for nonlinearity. Odds ratios for total IgE were calculated for the highest quartile compared to the lowest quartile. To study further the independent effects of sensitization to indoor and outdoor allergens on BHR, a logistic regression analysis was performed with different categories for sensitization to indoor allergens alone, outdoor allergens alone, and a combination of both.

Results

The study included 2711 subjects; 1927 subjects had complete data on bronchial responsiveness to methacholine, IgE measurements and smoking habits. From 619 subjects data on bronchial responsiveness were missing, from 214 subjects no blood was collected for IgE measurements and from 82 subjects data on smoking habits were not available. Characteristics from the current study subjects and from the subjects for whom information was missing are presented in Table 1. Subjects included in the present analyses were more frequently male and younger than subjects lacking information, and they had a lower mean total IgE level.

Sensitization to indoor and outdoor allergens according to age

The proportion of subjects with specific IgE class ≥ 2 decreased with increasing age, most obviously so for specific IgE to indoor allergens (Fig. 1). Specific IgE class ≥ 2 to both indoor and outdoor allergens had a rather high prevalence (15%) in the age group 20–29 years and was extremely rare (1%) in the age group 60–70 years (Fig. 1).

Age group 20–44 years. Subjects sensitized to outdoor allergens were more frequently sensitized to indoor allergens (class ≥ 2: 56%) than subjects not sensitized to

Table 1. Comparisons of subjects with and without complete information for data analysis

Characteristics	Complete	Incomplete
Number	1927	784†
Female, % (*n*)	48 (923)*	54 (424)
Age, mean (SD)	44 (14)*	50 (15)
Current smokers, % (*n*)	37 (714)	36 (250)
Bronchial hyperresponsiveness, % (*n*)	20 (380)	22 (37)
Specific IgE ≥ 1 allergen, % (*n*)	33 (627)	31 (175)
Total IgE, kU/l, geometric mean	30*	35

* $P < 0.05$ compared with subjects with incomplete information.
† Fluctuation in the number because of missing values.

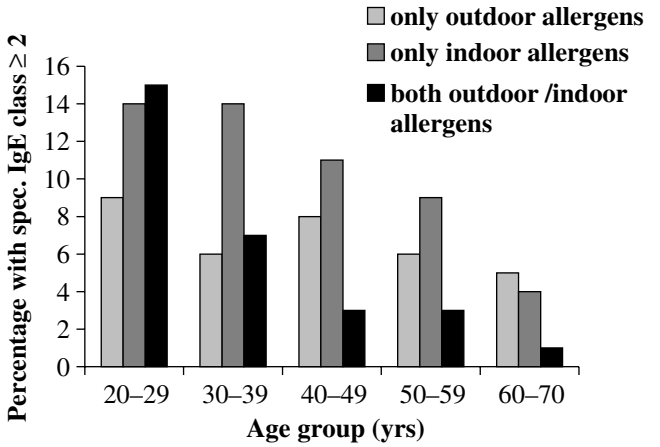

Figure 1. Prevalence of specific IgE class ≥ 2 to only outdoor allergens (timothy grass or birch), only indoor allergens (house dust mite or cat) or both for 10-year age groups.

outdoor allergens (class ≥ 2: 16%). For subjects who were sensitized to indoor allergens, the concurrent presence of sensitization to outdoor allergens was associated with higher classes of specific IgE to indoor allergens. The proportion of subjects with a level of specific IgE class 3 or higher to HDM was 66% among subjects sensitized to both indoor and outdoor allergens compared to 45% of the subjects sensitized to indoor allergens alone (for cat: 20% vs. 6%).

Age group 45–70 years. Only a higher prevalence (26% vs. 8%) but not a higher level (38% vs. 43% class ≥ 3 to HDM and 0% vs. 3% class ≥ 3 to cat) of sensitization to indoor allergens was found when sensitization to outdoor allergens was present.

Univariate association of BHR with allergic sensitization in relation to age

Age group 20–44 years. The prevalence of BHR was significantly higher in subjects with specific IgE to house dust mite (HDM) class ≥ 3 (47%) than in subjects without specific IgE to HDM (12%), whereas subjects with class 1 (13%) or class 2 (16%) had no higher prevalence of BHR (Table 2). Individuals with specific IgE to cat and timothy grass had significantly higher prevalences of BHR at levels of class 2 and ≥ 3 (Table 2) than those without specific IgE to these allergens. For birch pollen, only subjects with class 2 specific IgE expressed BHR more frequently (27%) compared to subjects without specific IgE (15%).

A high total IgE level, defined as a level in the highest quartile, was significantly associated with a higher prevalence of BHR compared to the lowest three quartiles (prevalences in quartiles 1–4: 12%, 13%, 13%, and 27%, respectively).

Age group 45–70 years. Similar univariate associations between BHR and specific IgE to indoor allergens were found as in the younger age group (Table 2). The prevalence of BHR was significantly higher in subjects with specific IgE to house dust mite (HDM) class ≥ 3 (44%) than in subjects without specific IgE to HDM (27%), whereas subjects with class 1 (22%) or class 2 (26%) had no higher prevalence of BHR (Table 2). Individuals with specific IgE to cat had significantly higher prevalences of BHR at levels of class 2 and ≥ 3 (Table 2) than those without specific IgE. No significant relation between specific IgE to timothy grass or birch pollen and BHR was found.

A high total IgE level, defined as a level in the highest quartile, was significantly associated with a higher prevalence of BHR compared to the lowest three quartiles (prevalences in quartiles 1–4: 16%, 23%, 21%, and 34%, respectively).

Table 2. Prevalence of bronchial hyperresponsiveness ($PD_{20} \leq 2$ mg) by degrees of sensitization for the age group 20–44 years, and 45–70 years

	Prevalence of BHR, % (number)			
	Indoor allergens		Outdoor allergens	
Specific IgE	HDM	Cat	Timothy grass	Birch
20–44 years				
No	12 (89)	14 (134)	14 (112)	15 (135)
Class 1	13 (8)	26 (6)	20 (12)	30 (13)
Class 2	16 (15)	47 (15)*	35 (21)*	27 (12)*
Class ≥ 3	47 (58)*	56 (15)*	32 (25)*	25 (10)
45–70 years				
No	22 (167)	22 (198)	23 (185)	24 (196)
Class 1	26 (15)	33 (3)	32 (15)	22 (6)
Class 2	27 (12)	64 (7)*	27 (8)	14 (4)
Class ≥ 3	44 (16)*	100 (2)*	11 (2)	18 (4)

* Difference from no specific IgE statistically significant ($P < 0.05$; Chi-squared test, 1 d.f.).

Multiple logistic regression analysis on bronchial hyperresponsiveness

Only the presence of specific IgE to indoor allergens was independently associated with the presence of BHR in the age group 20–44 years, odds ratio (OR) for specific IgE to house dust mite class ≥ 3 being 5.0 and to cat class ≥ 3 being 3.9, respectively (Table 3). In the age group 45–70 years, only specific IgE to cat class ≥ 2 was significantly associated with BHR (OR = 7.5). Specific IgE to the outdoor allergens timothy grass and birch was not significantly associated with BHR. A significant non-linear association between total IgE level and BHR was found in the oldest, but not in the youngest age group. Figure 2 illustrates the relation between total IgE and BHR after adjustment for specific IgE in both age groups.

When comparing outdoor with indoor allergens, specific IgE to outdoor allergens alone was not significantly associated with BHR in both age groups (Table 4). In the

Table 3. Odds ratios (95% confidence intervals) for bronchial hyperresponsiveness to methacholine with specific IgE and total IgE, adjusted for each other and current smoking, area of residence, age, and gender

	20–44 years ($n = 1018$)		45–70 years ($n = 909$)		20–70 years ($n = 1927$)	
Specific IgE	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
House dust mite						
No	738	1	771	1	1509	1
Class 1	63	0.9 (0.4–2.0)	57	1.3 (0.6–2.6)	120	1.0 (0.6–1.8)
Class 2	94	1.1 (0.6–2.2)	45	1.5 (0.7–3.1)	139	1.1 (0.7–1.8)
Class 3	123	5.0 (2.8–9.1)*	36	2.1 (0.9–5.0)	159	3.9 (2.4–6.1)*
Cat						
No	936	1	887	1	1823	1
Class 1	23	1.1 (0.4–3.2)	9	1.6 (0.3–8.7)	32	1.1 (0.5–2.7)
Class 2	32	2.3 (0.9–5.6)	11	7.5 (1.7–32.6)*	43	3.0 (1.4–6.2)*
Class 3	27	3.9 (1.5–10.0)*	2		29	5.3 (2.2–12.8)*
Timothy grass						
No	819	1	814	1	1633	1
Class 1	60	1.0 (0.5–2.2)	47	1.3 (0.6–2.9)	107	1.0 (0.6–1.8)
Class 2	60	1.8 (0.9–3.7)	30	0.9 (0.3–2.5)	90	1.3 (0.8–2.4)
Class 3	79	1.4 (0.7–3.0)	18	0.4 (0.1–1.9)	97	1.0 (0.5–1.9)
Birch						
No	891	1	832	1	1723	1
Class 1	43	1.9 (0.9–4.1)	27	0.5 (0.2–1.6)	70	1.2 (0.6–2.2)
Class 2	44	0.9 (0.4–2.2)	28	0.6 (0.2–1.9)	72	0.8 (0.4–1.5)
Class 3	40	0.7 (0.3–1.9)	22	0.5 (0.1–2.1)	62	0.6 (0.3–1.4)
Total IgE highest vs. lowest quartile	282	1.1 (0.8–1.7)	180	1.9 (1.4–2.7)*†	462	1.6 (1.2–2.0)*†

* Significant ($P < 0.05$).

† Significant non-linear relationship.

age group 20–44 years, specific IgE to indoor allergens alone was only associated with BHR at levels of class 3 or higher, whereas in the age group 45–70 years a level of class 2 was also significantly associated with BHR. The combination of specific IgE to indoor and outdoor allergens had the highest odds ratio for BHR in the age group 20–44 years.

Discussion

This study in a general adult population of 20–70 years shows as expected that sensitization to indoor allergens is associated with bronchial hyperresponsiveness. A new finding of our study is that in young adults, specific IgE levels to indoor allergens must be at least class 3 (20–44 years) to be associated with BHR, whereas in older subjects (45–70 years) lower levels of class 2 are sufficient. We also showed that it is important to recognize the close relationship between the presence of sensitization to outdoor allergens and the degree of sensitization to indoor allergens when studying the independent association of sensitization to pollen with BHR in young adults. Taking this into account, our study shows that subjects exclusively sensitized to grass or birch pollen do not show increased BHR at any level of sensitization. However, in young adults (20–44 year), multiple sensitization to both indoor and outdoor allergens is common and has a relatively strong association with BHR. In contrast, at an older age (45–70 year) multiple sensitization has a much lower prevalence and it has no significant association with BHR. Finally, this study shows that a significant dose–response relationship between serum total IgE and BHR is present only in the older age group.

Our results suggest that sensitization to the outdoor allergens timothy grass or birch pollen does not directly influence the presence of bronchial hyperresponsiveness, which is in agreement with the generally held opinion that pollen particles are too large to penetrate the lower airways. However, recent studies showed that, despite the fact that grass pollen grains are too large, they may be associated with atmospheric respirable particles (21). Thus, other explanations may be more relevant, such as different interactions of allergens with airway epithelial cells (22). House dust mite allergen is known to possess proteolytic activity, which promotes the penetration of allergens into the airway epithelium (22). This may also favour the trans-epithelial passage of other antigens and explain our finding that sensitization to outdoor allergens was only associated with BHR in young adults if they were also sensitized to indoor allergens. The observed significant univariate relationships between sensitization to outdoor allergens and BHR can be explained by the fact that, especially at a younger age, sensitizations to indoor and outdoor allergens are interrelated.

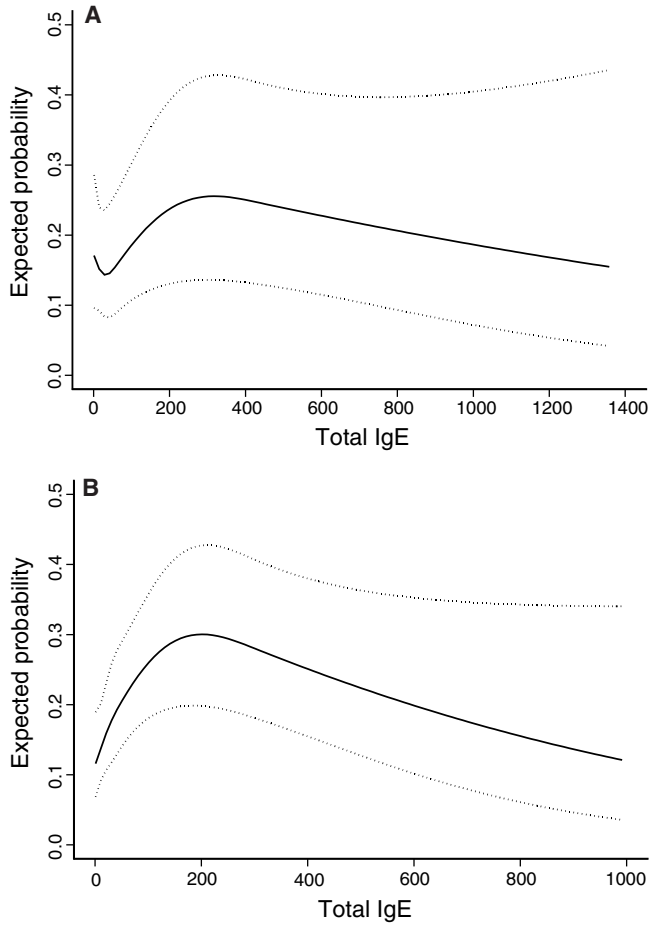

Figure 2. (A) Probability with 95% confidence intervals of BHR by level of total IgE for age group 20–44 years after adjustment for specific IgE (plotted from Restricted Cubic Spline function). (B) Probability with 95% confidence intervals of BHR by level of total IgE for age group 45–70 years after adjustment for specific IgE (plotted from Restricted Cubic Spline function).

To our knowledge, there is only one study that has observed a weak, but significant, association between sensitization to timothy grass alone and BHR, in a very large population of 11 215 subjects from 15 countries (15). The fact that we could not show such a weak association to be significant may be caused by the relatively small number of subjects exclusively sensitized to pollen in our study. Thus, the power of finding weak associations of BHR with sensitization to outdoor allergens, was limited in our study, especially at higher levels of sensitization. Two studies (10, 12), have found an independent relation between the presence of sensitization to grass pollen and BHR by multiple regression analysis. However, they did not fully account for the level of specific IgE to indoor allergens. Thus, the conclusion of these studies is disputable.

We found that a significant independent relationship between serum total IgE and BHR was present only in the older age group. In young adults the importance of serum total IgE as a determinant of BHR is difficult to evaluate, since the level of total IgE is closely related to the degree of sensitization to indoor allergens. At an older age, when sensitization is less prominent, an independent dose–response relationship between total IgE and BHR became visible in our data. Total IgE may reflect a genotype susceptible to allergic inflammation, of which the expression in the form of specific IgE to common inhalant allergens diminishes with increasing age. Some older subjects with a high total IgE level may have lost their specific IgE while BHR remained present. Indeed, longitudinal data from asthmatic subjects support the idea that skin test positivity may disappear with increasing age (23), while other longitudinal studies have suggested that total IgE tracks with age (24, 25).

A diminishing degree of sensitization with aging may also explain our finding that specific IgE class 2 to indoor allergens was significantly associated with BHR in the

Table 4. Odds ratios (95% confidence intervals) for bronchial hyperresponsiveness with specific IgE class to indoor and/or outdoor allergens, adjusted for each other and total IgE, current smoking, area of residence, age, and gender

	20–44 years ($n = 1018$)		45–70 years ($n = 909$)		20–70 years ($n = 1927$)	
	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*
	Reference	715	Reference	763	Reference	1478
Indoor negative† and						
outdoor class 2	0.9 (0.3–3.2)	27	0.7 (0.3–2.0)	33	0.7 (0.3–1.6)	60
outdoor class ≥ 3	1.8 (0.8–4.2)	45	0.4 (0.1–1.5)	27	0.9 (0.5–1.9)	72
Outdoor negative and						
Indoor class 2	0.8 (0.3–1.8)	71	2.2 (1.0–4.7)*	36	1.2 (0.7–2.0)	107
Indoor class ≥ 3	6.5 (3.5–12.0)*	69	3.0 (1.3–6.8)*	29	4.4 (2.7–7.0)*	98
Both indoor and outdoor positive and						
both class 2	3.0 (0.6–14.8)	10	0.6 (0.1–3.7)	8	1.4 (0.4–4.9)	18
at least one class ≥ 3	7.7 (4.2–14.2)*	81	1.4 (0.4–4.7)	13	5.4 (3.3–9.0)*	94

* Significant ($P < 0.05$).
† Negative = class 0 or 1.

older age group, whereas no association was found in young adults.

Another explanation of the association between total IgE and BHR at an older age may be that this indicates the effect of sensitization to other unknown allergens at an older age.

Although the proportion of cases with BHR attributable to sensitization will be lower at an older age, allergy still plays a role. The strength of the association between sensitization to indoor allergens alone and BHR was similar for younger and older subjects. Thus, in clinical practice, the possibility must be considered that even older patients with BHR may benefit from reduction in exposure to indoor allergens.

From the original sample of 4522 subjects who were invited to the examination, 2711 subjects responded. The results of a postal screening questionnaire sent to all the subjects before they were invited to the examination, showed that the prevalence of self-reported asthma or nasal allergy was not different in subjects who responded compared to non-responders. Complete data for the current analyses were available only for 1927 subjects. This secondary loss of subjects was in most cases caused by the exclusion criteria for methacholine provocation. Table 1 shows that this has probably led to some bias in prevalences of health outcomes, which might have influenced the results. However, selection bias is less likely to occur when studying associations than prevalences. In the current analyses, selection bias may only have occurred when the probability of having complete data is related to the presence of BHR and furthermore that this relation is different depending on the presence of sensitization.

In conclusion, our observation that sensitization to indoor allergens, as opposed to sensitization to outdoor allergens alone, is associated with bronchial hyperresponsiveness, supports the causal role of allergy in BHR and disagrees with the idea that allergy is an epiphenomenon of BHR. The findings that total IgE has a dose–response relationship with BHR only at an older age and that sensitization to indoor allergens is also related to BHR in older subjects, even at lower levels, indicates that the role of allergy for the presence of BHR at an older age may be less pronounced but still relevant.

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