

Aeroallergen and food IgE sensitization and local and systemic inflammation in asthma

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aeroallergens; airway responsiveness; blood eosinophil count; exhaled nitric oxide; food allergens.

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Abstract

Background: We recently reported an independent association between IgE sensitization to food allergens and increased airway inflammation, assessed by fraction of exhaled nitric oxide (FeNO), in a population-based study (*J Allergy Clin Immunol*, **130**, 2012, 397). Similar studies have not been performed in populations with asthma. The aim of the present study was to investigate the allergic sensitization profile in asthmatics and examine FeNO, airway responsiveness and blood eosinophilia in relation to type and degree of IgE sensitization.

Method: FeNO, airway responsiveness, blood eosinophil count (B-Eos) and IgE sensitization to food allergens and aeroallergens were determined in 408 subjects with asthma, aged 10–34 years.

Results: Asthmatics had higher prevalence of IgE sensitization against all allergens than controls ($P < 0.001$). Mite, pollen, furry animal, mould and food sensitizations were each associated with increased FeNO, airway responsiveness and B-Eos in asthmatics. IgE sensitization to mould, furry animals and food allergens was independently related to FeNO (all $P < 0.05$) after adjustment for age, sex, height, smoking history and medication. IgE sensitization to mould ($P < 0.001$) and furry animals ($P = 0.02$) was related to airway responsiveness in a similar model. Finally, IgE sensitization to mould ($P = 0.001$), furry animals ($P < 0.001$) and food allergens ($P < 0.001$) was independently related to B-Eos.

Conclusion: Independent effects of IgE sensitization to aeroallergens (furry animals and mould) and food allergens were found on both local and systemic markers of inflammation in asthma. The finding regarding food IgE sensitization is novel, and a clinical implication might be that even food sensitization must be assessed to fully understand inflammation patterns in asthma.

Asthma is a significant health problem affecting 300 million people (1). Atopy is an important risk factor for asthma (2), and about 70% of Sweden's asthmatics (3) are atopic. Airway inflammation and hyper-responsiveness are key pathophysiological features (1) underlying asthma. The level of

exhaled nitric oxide (FeNO), a marker of airway inflammation (4), is increased in asthma. FeNO (5, 6) and airway hyper-responsiveness are also related to IgE sensitization (7).

Aeroallergen IgE sensitization does not predict asthma in an all-or-nothing fashion. Rather, the specific pattern (8) and degree (9) of IgE sensitization are linked to the probability of developing asthma and other atopic disease. Furthermore, we have recently shown that not only aeroallergen sensitization, but also food IgE sensitization, is linked to increased FeNO and increased risk for asthma (3). IgE sensitization to food is highly prevalent in adults (10) as well as children (11) with asthma and is associated with increased use of healthcare and

Abbreviations

B-Eos, blood eosinophil count; BMI, body mass index; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in one-second; FVC, forced expiratory volume; MIDAS, Minimally Invasive Diagnostics for Asthma and allergic diseaseS; PD₂₀, cumulative dose of methacholine causing a 20% reduction in FEV₁.

asthma medication (11). Sensitization to food allergens also correlates with the severity of atopic dermatitis in children (12).

Peripheral blood eosinophilia is generally recognized as a feature of asthma (13). However, children with food allergy also have increased numbers of eosinophils in blood (14), and a significant correlation between food sensitization and blood eosinophils has been found in a population-based study of adults (10).

The relative importance of food and aeroallergen IgE sensitization for airway inflammation and responsiveness and for systemic eosinophilic inflammation has not been studied previously in asthmatics. The interrelationship between local drivers of inflammation (aeroallergens) and drivers located elsewhere (e.g., in the gut), but that may also affect the airways, may be important information to have at hand when trying to find optimal asthma treatment.

The aim of this study was to investigate the IgE sensitization profile in asthmatics and to examine the association between this profile and exhaled nitric oxide, blood eosinophil count (B-Eos) and airway responsiveness to methacholine.

Methods

Population description

The study was based on subjects who participated in a project run within the framework of an industry-academy collaboration on Minimally Invasive Diagnostics for Asthma and allergic diseases (MIDAS). Subjects were recruited from both primary and specialist care in Uppsala, Sweden. The MIDAS study included 411 children and young adults (10–34 years) with physician-diagnosed asthma (according to their medical record) and daily treatment with inhaled corticosteroids and/or oral antileukotrienes during at least 3 months of the year before the study. It also included 118 nonasthmatic controls randomly chosen from the population registry. Subjects reporting ever having received asthma diagnosis or used asthma medication or having a chronic respiratory disease were excluded from the control group.

The present study included only those subjects from whom blood samples were available for the characterization of IgE sensitization (a total of 408 asthmatic individuals and 118 nonasthmatic subjects).

Lung function

Flow-volume curves were performed using a MasterScope spirometer (Erich Jaeger, Wurzburg, Germany). Subjects performed three technically acceptable trials, according to the ATS/ERS recommendations (15), and the highest values for forced expiratory volume (FVC) and forced expiratory volume in one-second (FEV₁) were recorded.

Height, weight and BMI

Height and weight were measured the same day as the lung function tests were performed. BMI was calculated by dividing weight by the square of height.

Smoking history

Smoking history was assessed by questionnaire. Current smokers were individuals with a history of smoking >1 pack-year and reporting current smoking of at least 1 cigarette/day during the last 6 months prior to the study.

Asthma symptoms and medication

Subjects participated in a detailed interview containing questions regarding symptoms of asthma, rhinitis and sinusitis as well as medication use. The asthma symptom questionnaire included wheezing; chest tightness; shortness of breath at night, during rest or during exercise; and asthma attacks during the last 12 months (16).

The degree of asthma control was assessed using Asthma Control Test (ACT) (17), which is a questionnaire consisting of five questions, each with a 5-point scale. The total ACT score is between 5 and 25, with a lower score indicating poorer control of asthma. An ACT score >20 reflects well-controlled asthma (17).

Presence and degree of IgE sensitization

IgE levels against a mix of food allergens (fx5), hazelnut, shrimp, peach, a mix of aeroallergens (Phadiatop) and *Alternaria alternata* were measured in all subjects. Subjects with titres of ≥ 0.35 kU/l against the aeroallergen or food mix were further characterized regarding IgE antibody levels against each individual allergen of the respective panel: egg white, milk, cod fish, wheat, peanut and soybean for the food allergen panel and cat, dog, horse, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Cladosporium herbarum*, birch, timothy grass and mugwort for the aeroallergen panel. All measurements of IgE were taken using ImmunoCAP system (Immunodiagnosics; Thermo Fisher Scientific, Uppsala, Sweden). The results are presented in kU/l and values of IgE ≥ 0.35 kU/l for an individual allergen defined a subject as being sensitized to that allergen (18). Subjects with IgE antibody levels <0.35 kU/l were given an arbitrary value of 0.17 kU/l. The IgE antibody levels were added up (sum IgE) (5) to make an assessment of the overall level of IgE sensitization in five different allergen categories:

1. Mite (*D. pteronyssinus*, *D. farinae*),
2. Mould (*C. herbarum*, *A. alternata*/ *Alternaria tenuis*),
3. Furry animal (cat, horse, dog),
4. Pollen (timothy, birch, mugwort) and
5. Food (wheat, peanut, soy, shrimp, egg, milk, fish).

We chose not to include hazelnut and peach when evaluating the results in the group of food allergens due to the large extent of cross-reactivity in birch-sensitized subjects with hazelnut (94%) and peach (73%). In order to adjust for a potential cross-reactivity between horse and cat IgE (19), we have performed additional analyses after removing subjects sensitized to horse from the group sensitized to furry animals.

Exhaled NO

FeNO measurements were performed according to American Thoracic Society/European Respiratory Society recommendations (20) using a chemiluminescence analyser (NIOX[®] Flex; Aerocrine AB, Solna, Sweden). Measurements were taken in duplicates in the sitting position using a single-breath technique after inhaling NO-free air from a scrubber, and the mean value was calculated. If the difference between individual measurements exceeded 10%, additional measurements were taken. Subjects were instructed not to drink or eat during 30 min prior to NO measurements, as well as to avoid smoking, using oral tobacco and drinking beverages containing caffeine. Subjects were also instructed to avoid eating large quantities of green-leaved vegetables and to avoid intensive physical exercise on the day of the measurements. The analyser was calibrated every 14 days with certified NO/N₂ gas of 200 ppb according to the manufacturer's recommendations.

Methacholine challenge test

A bronchial provocation test was performed with Aerosol Provocation System (Viasys Healthcare GmbH, Hoechst, Germany) according to a simplified protocol, using a single concentration of methacholine and stepwise increasing doses up to a maximal cumulative dose of 3.63 mg methacholine (21). Two minutes after each inhalation, FEV₁ was measured and PD₂₀ FEV₁ (the cumulative dose of methacholine causing a 20% reduction in FEV₁) was calculated by logarithmic interpolations using an integrated program. Subjects refrained from using asthma and allergy medication for 24 h before the study.

Blood eosinophil count

Blood eosinophil count was made at the Department of Clinical Chemistry, Uppsala University Hospital, using a routine method (Cell-Dyn Sapphire, Abbott, IL, USA).

Statistics

Statistical analyses were performed using STATA 12.1 software (Stata Corp., College Station, TX, USA). Unpaired *t*-test (for numerical variables) and Pearson's chi-squared test (for categorical variables) were used to compare FeNO, PD₂₀, B-Eos and prevalence of IgE sensitization to various allergens in asthmatics and controls. Unpaired *t*-test was used to compare log-transformed levels of FeNO, PD₂₀ and B-Eos against sensitization or not to each food allergen and aeroallergen investigated and to the five groups of allergens. Interaction between age or sex and FeNO, PD₂₀ and B-Eos was studied in asthmatics sensitized to a group of allergens by multiple linear regression models.

We used percentage difference in FeNO, PD₂₀ and B-Eos as measure of effect. Percentage difference in FeNO, PD₂₀ and B-Eos was obtained from linear regression models where the log-transformed value was the outcome variable. The regression coefficient for the predictor variable of interest (e.g., food

sensitization) was back-transformed, as described in previous studies (22), in order to obtain the fold difference in FeNO, PD₂₀ and B-Eos (e.g., food sensitized vs. non-food-sensitized), and this was in turn converted to percentage difference by multiplying the obtained fold difference by 100 and subtracting 100%. We estimated % difference in FeNO, PD₂₀ and B-Eos for every 1% increase in grade of IgE sensitization, by back-transforming the regression coefficient from the model where both outcome and predictor were log-transformed (23). A *P*-value of <0.05 was considered statistically significant.

Ethics

Written informed consent was obtained from each subject before inclusion in the study. The study was approved by the Regional Ethics Committee in Uppsala (2009/349).

Results

The characteristics of the asthma and control groups are shown in Table 1. Asthmatics had poorer lung function and smoked less than the controls. FeNO, airway responsiveness and B-Eos were higher in asthmatics. The prevalence of sensitization to all allergens was higher among the asthmatics than among controls (Table 2). Cat, dog and birch were the most prevalent allergens in asthmatics, whereas hazelnut, birch and timothy were the most prevalent in controls. Generally, the levels of IgE towards a specific allergen were higher in sensitized asthmatics than in controls, but this reached a statistical significance only for dog, birch, hazelnut and peach (Table 2).

Association between IgE sensitization and FeNO, airway responsiveness and B-Eos in asthmatics

FeNO, airway responsiveness and B-Eos were higher in sensitized compared to nonsensitized asthmatics for all groups of allergens (Table 3).

Table 1 Characteristics of participants [mean ± SD, %, geometrical mean (95% CI) and median (IQR)]

	Asthma (<i>n</i> = 408)	Controls (<i>n</i> = 118)	<i>P</i> -value
Age (years)	20.4 ± 7.1	20.4 ± 6.1	0.66
Women	50.9	54.6	0.48
BMI	22.6 ± 4.3	22.0 ± 3.3	0.23
FEV ₁	92.0 ± 14.2	96.9 ± 13.5	0.005
Current smokers	4.2	9.3	0.03
FeNO (ppb)	16 (15, 17)	12 (11, 14)	<0.001
PD ₂₀ (mg)	0.43 (0.35, 0.53)	1.49 (1.05, 2.11)	<0.001
B-Eos (×10 ⁹ l)	0.18 (0.17, 0.20)	0.12 (0.10, 0.14)	<0.001
ACT	21 (19, 23)	NA	
Inhaled steroids (µg/day)	320 (160, 400)	0 (0, 0)	<0.001
Antileukotrienes	18	0	<0.001

ACT, Asthma Control Test; B-Eos, blood eosinophil count; NA, not applicable.

Table 2 Prevalence of IgE sensitization to individual allergens and levels of IgE to sensitized subjects in asthmatics and nonasthmatics (%)

	Asthma (n = 408)		Controls (n = 118)		P-value†	P-value‡
	Prevalence	Level of IgE in sensitized subjects*	Prevalence	Level of IgE in sensitized subjects*		
<i>Dermatophagoides pteronyssinus</i>	27.0	2.1 (1.6, 2.7)	8.4	0.8 (0.4, 1.9)	<0.001	0.057
<i>Dermatophagoides farinae</i>	24.8	2.5 (1.8, 3.4)	6.7	1.1 (0.4, 3.1)	<0.001	0.17
<i>Cladosporium herbarum</i>	14.5	4.0 (2.7, 5.9)	0.8	0.4	<0.001	NA
<i>Alternaria alternata/Alternaria tenuis</i>	12.0	1.6 (1.1, 2.4)	1.7	0.6 (0.3, 1.2)	<0.001	0.27
Cat	56.1	8.3 (6.6, 10.5)	11.8	3.7 (1.9, 7.0)	<0.001	0.09
Horse	41.7	5.5 (4.1, 7.1)	5.0	1.4 (0.1, 20.1)	<0.001	0.06
Dog	60.3	4.4 (3.6, 5.3)	14.3	1.3 (0.7, 2.3)	<0.001	0.002
Timothy	54.4	3.0 (1.5, 6.1)	18.5	5.8 (4.6, 7.2)	<0.001	0.08
Birch	55.9	11.0 (8.9, 13.6)	19.3	4.8 (2.5, 9.2)	<0.001	0.02
Mugwort	26.5	2.2 (1.7, 2.9)	7.6	1.4 (0.4, 4.3)	<0.001	0.30
Hazelnut	53.9	8.9 (7.2, 11.0)	20.2	2.9 (1.6, 5.1)	<0.001	0.0012
Shrimp	14.7	1.4 (1.1, 2.0)	3.4	0.4 (0.3, 0.6)	<0.001	0.056
Peach	41.4	2.2 (1.8, 2.6)	11.8	1.1 (0.6, 1.9)	<0.001	0.04
Egg	11.8	2.4 (1.5, 3.7)	2.5	0.5 (0.3, 0.6)	<0.001	0.078
Milk	11.5	2.1 (1.3, 3.6)	0.8	0.6	<0.001	NA
Fish	5.9	3.0 (1.6, 5.8)	0	0	<0.001	NA
Wheat	16.7	1.5 (1.2, 2.0)	3.4	0.8 (0.1, 4.9)	<0.001	0.25
Peanut	24.8	9.2 (6.1, 13.9)	2.5	1.1 (0.0, 24.0)	<0.001	0.08
Soy	18.1	2.0 (1.4, 2.7)	2.5	0.8 (0.1, 13.6)	<0.001	0.27

NA, nonapplicable.

*Geometrical mean (95% CI).

†Between prevalence.

‡Between levels of IgE of sensitized subjects.

FeNO was independently associated with the presence of IgE (≥ 0.35 kU/l) against mould, furry animals and food after adjustment for type of sensitization, age, sex, height, smoking history and medication. Similarly, airway responsiveness was independently associated with having IgE against mould and furry animals, whereas B-Eos was independently associated with the presence of IgE against mould, furry animals and food (Fig. 1). Furthermore, FeNO was independently associated with the degree (sum IgE) of furry animal and food IgE sensitization; airway responsiveness was independently associated with the degree of mould and furry animal IgE sensitization; and B-Eos was independently associated with the degree of mould, furry animal and food IgE sensitization (Table 4). The results above were consistent after excluding horse sensitization from the group sensitized to furry animals or from the sum of IgE against furry animals.

We examined the interaction of being a child (<18 years) or adult (≥ 18 years) with the relationship between type of sensitization and FeNO, airway responsiveness and B-Eos. Significant interaction was found regarding the relationship between furry animal sensitization and FeNO ($P = 0.003$); the percentage FeNO difference in furry animal-sensitized adults was 38.5% (8.4, 77.0), while in children this difference was 93.3% (42.9, 161.5). A significant interaction was found also regarding the relationship between food sensitization and B-Eos ($P = 0.03$); the percentage B-Eos difference in food-sensitized adults was 26.3% (-3.4, 65.0) and in children 54.2% (15.6, 105.6).

There was no significant sex-related interaction between type of IgE sensitization and FeNO, airway responsiveness and B-Eos.

Discussion

The main findings of this study were the independent effects of presence and degree of IgE sensitization to aeroallergens (furry animals and mould) and food allergens on both local and systemic markers of inflammation in asthma. To our knowledge, this is the first study to examine the association between different types of IgE sensitization, including food IgE sensitization, and the level of local and systemic inflammation in children and young adults with asthma. Our results show that food IgE sensitization plays a role both for local airway inflammation and for systemic inflammation in this asthmatic population.

The markers of local inflammation, FeNO and airway responsiveness were independently associated with the presence (titre ≥ 0.35 kU/l) of mould and furry animal IgE sensitization and independently associated with the degree of furry animal IgE sensitization in the present material. Additionally, presence and degree of IgE sensitization to food allergens were both associated with FeNO. FeNO has previously been reported to be increased in asthmatic children sensitized to furry animals (24) and is also associated with the degree of IgE sensitization to furry animals in asthmatic children (24) and adults (6). Mould sensitization was related to

Table 3 Effects of IgE sensitization in asthmatics on FeNO [geometrical mean (95% CI)], airway responsiveness (PD₂₀) [geometrical mean (95% CI)] expressed as dose-response slope to methacholine challenge, where a lower value indicates more responsiveness, and blood eosinophil count (B-Eos) [geometrical mean (95% CI)]

	FeNO (ppb) (<i>n</i> = 407)				PD ₂₀ (mg) (<i>n</i> = 373)				B-Eos ($\times 10^9$ ℓ) (<i>n</i> = 407)			
	Sensitized				Sensitized				Sensitized			
	N sens	Yes	No	P-value	N sens	Yes	No	P-value	N sens	Yes	No	P-value
Mite	117	19.3 (16.8, 22.2)	14.4 (13.2, 15.7)	<0.001	114	0.31 (0.20, 0.49)	0.50 (0.39, 0.64)	0.049	117	0.25 (0.21, 0.30)	0.16 (0.14, 0.17)	<0.001
Mould	74	22.8 (19.1, 27.4)	14.4 (13.3, 15.7)	<0.001	62	0.13 (0.08, 0.20)	0.56 (0.45, 0.72)	<0.001	75	0.33 (0.28, 0.40)	0.16 (0.14, 0.17)	<0.001
Pollen	281	17.8 (16.2, 19.4)	11.9 (10.5, 13.6)	<0.001	248	0.36 (0.27, 0.47)	0.70 (0.50, 0.97)	0.005	281	0.20 (0.18, 0.22)	0.14 (0.12, 0.16)	<0.001
Furry animals	268	19.5 (17.8, 21.3)	10.3 (9.2, 11.5)	<0.001	236	0.31 (0.23, 0.40)	0.88 (0.64, 1.2)	<0.001	268	0.22 (0.20, 0.25)	0.12 (0.11, 0.14)	<0.001
Food	148	21.0 (18.7, 23.6)	13.3 (12.1, 14.6)	<0.001	125	0.22 (0.16, 0.32)	0.62 (0.48, 0.81)	<0.001	149	0.28 (0.24, 0.31)	0.14 (0.13, 0.16)	<0.001

N sens, Number of sensitized subjects.

high FeNO levels in a population-based study (5). The levels of FeNO were significantly higher in patients with asthma who were both sensitized and exposed to relevant aeroallergen (to mite, cat or dog) than in those who were sensitized, but not exposed (25). However, in the present study, mite sensitization was not related to increased FeNO, which probably reflects the low exposure to mite allergen in Sweden (26).

Our previous population-based study showed an independent association of perennial (furry animal, mite and mould) IgE sensitization with airway responsiveness (3). Mould sensitization was the type of sensitization associated with the largest increase in airway responsiveness in our material, and previous studies have shown that mould sensitization is associated with more severe asthma in young adults (27) or admission to intensive care unit (28). This may be supported by data from animal models showing that exposure to mould aggravates Th2-driven airway inflammation, promotes airway remodelling and increases airway responsiveness in ovalbumin-sensitized and challenged rats (29). However, mould exposure levels used in the above-named study are difficult to compare to that occurring in homes in Uppsala.

IgE sensitization to food allergens was also independently associated with increased FeNO, but not with airway responsiveness in adults in our previous population-based study (3). A recent study (30) reported an increased airway inflammation, measured as FeNO or sputum eosinophils, in children with asthma and food allergies compared to children with asthma alone.

The prevalence of food IgE sensitization is up to 45% in asthmatics (11, 31), but its influence on inflammation and asthma has not been studied until now. Although we have no data on food allergen exposure in our study population, it is reasonable to assume that only a minority (about one-tenth) of the subjects with IgE antibodies towards a food allergen have symptoms of food allergy (31) and therefore avoid the food in question. Mechanistically, exposure of the gastrointestinal tract to food allergens may drive inflammation in primed tissue in the airway mucosa in subjects sensitized to both aeroallergens and food allergens. Additionally, some of the food allergens may be inhaled and exposure to aerosolized food has been reported to result in asthma symptoms in asthmatic children with food allergies (32). The differences between associations of IgE sensitization with FeNO, on the one hand, and methacholine responsiveness, on the other hand, are in line with the moderate correlations reported between FeNO and airway responsiveness to methacholine in asthmatics (33). FeNO signals local IL-4/IL-13-mediated mechanisms in the bronchial mucosa, primarily triggered by aeroallergen exposure (34), whereas airway responsiveness to methacholine also reflects ongoing airway remodelling and structural changes in chronic asthma (35).

The marker of systemic eosinophil inflammation used in the present study, that is, the number of blood eosinophils, was independently associated with the presence of IgE sensitization to mould, furry animals and food and was also independently associated with the degree of mould, furry animal and food IgE sensitization. Development of eosinophilia is

Table 4 Independent association (in asthmatics) between degree of IgE sensitization (sum of specific IgE titres) against groups of allergens and FeNO, airway responsiveness (PD₂₀) expressed as dose-response slope to methacholine challenge, where a negative value indicates more responsiveness and blood eosinophil count (B-Eos)

	FeNO* [% difference (95% CI)]†	P-value	PD ₂₀ [% difference (95% CI)]†	P-value	B-Eos [% difference (95% CI)]†	P-value
Mite	−0.6 (−4.7, 3.7)	0.8	0.5 (−11.1, 13.7)	0.9	1.3 (−3.3, 6.4)	0.6
Mould	0.9 (−3.7, 5.7)	0.7	−14.1 (−25.2, −1.3)	0.03	6.0 (0.6, 11.7)	0.03
Pollen	1.6 (−2.8, 6.1)	0.5	3.8 (−8.9, 18.2)	0.6	1.5 (−3.3, 6.6)	0.5
Furry animals	12.7 (8.2, 17.4)	<0.001	−18.6 (−27.9, −8.0)	0.001	10.8 (5.8, 16.0)	<0.001
Food	7.4 (2.0, 13.2)	0.007	−6.3 (19.9, 9.7)	0.4	9.4 (3.2, 16.0)	0.003

*No. of subjects sensitive to respective allergen among asthmatics with FeNO (*n* = 317), PD₂₀ (*n* = 281) or B-Eos (*n* = 317).

†Adjusted for the variables in the table and age, sex, height, smoking history, use of inhalant corticosteroids and use of antileukotrienes.

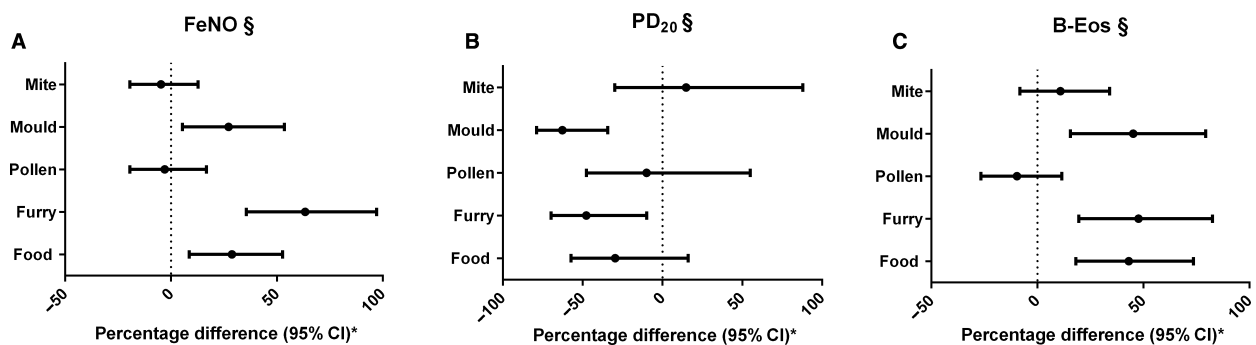


Figure 1 Independent association expressed as [% difference (95% CI)]* in FeNO (Panel A), airway responsiveness (PD₂₀) (Panel B) and blood eosinophil count (B-Eos) (Panel C) between subjects sensitized and nonsensitized to specific allergen groups. [Significant difference (*P* < 0.05) means that the line of error bars

does not cross the zero-percentage difference line.] *Adjusted for the variables in the figure and age, sex, height, smoking history, use of inhalant corticosteroids and use of antileukotrienes. §No. of subjects sensitive to respective allergen among asthmatics with FeNO (*n* = 402), PD₂₀ (*n* = 352) or B-Eos (*n* = 402).

common in asthmatics with mould sensitization (36). Current exposure to furry animals also associates with blood eosinophilia (37), and multisensitization to furry animal-derived components associates with increased numbers of blood eosinophils in patients with severe asthma (38). The relationship between food allergen sensitization and eosinophilia has not been studied previously in asthmatics although such a relationship has been reported in a population-based study of adults (10) and in children with food allergy (14) or atopic dermatitis (39). The systemic eosinophilic inflammatory component is of importance for asthma, as the number of eosinophils in peripheral blood and in bronchial lavage from subjects with asthma is associated with disease severity (40), and we have recently reported that the information from B-Eos [which signals an inflammatory pathway primarily driven by IL-5 (41)] is additional to the information from FeNO, when predicting wheeze or asthma events in the normal population (42).

The strength of this study is the detailed characterization of the IgE sensitization profile, including food IgE sensitization, a component often not assessed, in a cohort of children and young adults with asthma. Simultaneous analyses of exhaled nitric oxide, airway responsiveness and B-Eos were

available for the subjects of this study. We could confirm in the present asthma population the previously reported associations between food IgE sensitization and local and systemic inflammation in population-based studies (3, 10). However in these above-named studies, the prevalence of asthma was <20% and no subanalyses were performed for the asthmatic subjects. It is reasonable to believe that both local and systemic Th2 cytokine-driven mechanisms are involved in asthma. There seems to be additional information in assessing local and systemic inflammation, as we have previously reported that measurements of FeNO and B-Eos provide an additive and independent information in relation to wheezing, asthma and asthma attacks in subjects who participated in the National Health and Nutrition Examination Survey 2007–2010 (42). Furthermore, blood eosinophilia has been associated with asthma attacks also in other studies (43). B-Eos can be driven by other mechanisms, such as rhinovirus infections (44) or chronic rhinosinusitis (45). Therefore, it may be important to map out the sensitization profiles as triggers of local and systemic inflammation, in order to enable personalized, biomarker-based treatment of patients with asthma. Our study is the first one, to our knowledge, to incorporate both measures of local and systemic airway

inflammation and study them in relation to patterns of IgE sensitization. However, a weakness of our study is the lack of data on exposure to allergens, especially food allergens, as it is reasonable to believe that exposure influences inflammation in subjects sensitized to relevant allergens. The use of component-resolved diagnosis could have given more information regarding cross-reactivities. Simply summing up IgE titres against different allergens does not take into account primary sensitization vs cross-reactivities. Furthermore, it would have allowed us to analyse whether some allergen components for the same allergen are more important than others in relation to local and systemic inflammation.

We conclude that the level of biomarkers of local and systemic inflammation in asthmatics is independently associated with IgE sensitization to both aeroallergens (furry animals and mould) and food allergens. These findings indicate that both aeroallergen and food sensitization should be mapped to be able to fully understand the signalling of local markers of inflammation and airway responsiveness as well as the added value of measurement of systemic eosinophilic inflam-

mation. The clinical implications of these results, for example, with regard to optimization of treatment or importance of allergen avoidance in food-sensitized subjects with asthma warrant further research.

Conflicts of interest

The MIDAS study was supported within an industry-academy collaboration framework initiated by the Swedish Governmental Agency for Innovation Systems (VINNOVA, SAMBIO program, grant number 2007-00084) where Aero-crine AB (producer of exhaled NO devices), Thermo Fisher Scientific, Immunodiagnosics (producer of allergy tests) were partners and cofinanced the program. AP had financial support from Bror Hjerpstedts Foundation. AM had support from Uppsala University Hospital. None of the funding agencies or industry partners had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. KA and MB participated in their roles as adjunct professors at the university.

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