

# Bronchial reactivity in school children with food allergy in infancy

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## Abstract

**Introduction:** Sensitization to food allergens in early childhood is a risk factor for airborne sensitization and the development of asthma later in life. What underlies this phenomenon is not exactly known so far. It is also not clear what mechanism may predispose children with food allergies to develop asthma later in life.

**Aim:** To assess bronchial hyperreactivity in school-age children with food allergy in infancy.

**Material and methods:** This retrospective study included 158 children aged 7-18 years, who were diagnosed due to the suspicion of allergy in the Department of Allergology, Gastroenterology and Nutrition, Medical University of Lodz. The study was conducted on children suffering from atopic dermatitis, asthma or allergic rhinitis, in which parents reported the presence of food allergy in infancy. The methodology used: a questionnaire survey, medical examination, skin tests (Allergopharma, Reinbek, Germany), spirometry (spirometer Lungtest 1000, MES), and methacholine provocation tests (MP Biomedicals), using inhalant allergy Provocations System MES.

**Results:** A positive result of the methacholine challenge test was obtained in 33, i.e. in 63.5% of children in the study group and in 30 children (50%) in the control group ( $p > 0.05$ ). Bronchial hyperreactivity occurred significantly more often in children with asthma (20 children, i.e. 95.2%) compared to children with atopic dermatitis (7, i.e. 43.7% of children), as well as compared to children with rhinitis (6 or 40% children) in the study group ( $p < 0.001$ ,  $p < 0.004$ ). The degree of bronchial hyperreactivity in both the study group and control group was similar. Sensitization to food allergens affected 23 children (44.2%) in the study group and 18 children (30%) in the control group ( $p > 0.05$ ).

**Conclusions:** Airway hyperresponsiveness in school children with allergic diseases is not directly dependent on food allergy in infancy.

**Key words:** bronchial hyperreactivity, food allergy, children.

## Introduction

Bronchial hyperreactivity is an increased tendency of the respiratory tract to perform bronchospasm having been exposed to various immunological (allergens) and non-immunological (pharmacological, chemical and physical) stimuli, which do not cause any reactions in most healthy people [1]. The prevalence of non-specific bronchial hyperreactivity depends on latitude and it is estimated that in the general population 16-30% of children and 10-16% of adults are affected by it [2, 3]. Bronchial hyperreactivity is a characteristic feature for bronchial asthma. It may, however, occur in other diseases and pathological states such as: mucoviscidosis, sarcoidosis, allergic pul-

monary alveolitis, recurrent pneumonia, circulatory insufficiency, viral infection of the upper respiratory tract or atopic dermatitis and allergic rhinitis [4-6]. It has been proved that bronchial hyperreactivity may occur in patients with diseases of the alimentary tract such as non-specific inflammatory bowel disease or isolated food allergy [7-11], as well as in 5-10% of healthy people [12].

Results of scientific studies show that the relation between food allergy and asthma is becoming more and more significant. It has been proved that children manifesting symptoms of food allergy much more frequently suffered from asthma than children who did not manifest such symptoms [13-15]. It has also been stated that infants with IgE-dependent cow's milk allergy will continue to have

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allergy to these proteins and will probably become sensitized to other food allergens more often than other children [16]; moreover, sensitization to food allergens in early childhood is a risk factor for airborne sensitization and the development of asthma later in life [17-19]. Nickel states that egg-specific IgE antibodies in the 12<sup>th</sup> month of life are a valuable marker which might be helpful in prediction of asthma, atopic dermatitis and allergic rhinitis in later life [16]. After examining a population of 800 children it was proved that children with symptoms of atopic dermatitis and food allergy in the first three years of life manifest higher risk of developing asthma in puberty. The authors imply that as a result of synergistic interaction between the impaired skin barrier related to filaggrin gene mutation and food allergy in early life, the risk of occurrence of asthma is much higher [20]. Moreover, recent experiments on mice showed that activated T-lymphocytes of intestinal mucosa in the course of food allergy stimulate cells of bronchial mucosa and in that way they increase their reactivity [21]. Besides, the inflammatory process in the alimentary tract intensifies allergic reactions of the respiratory system, not only to sensitizing food allergens but also to non-related inhaled allergens [22].

With age most children become more tolerant to food allergens but at the same time they manifest symptoms of allergic diseases of the respiratory system. This phenomenon is commonly known as "allergic march" [16]. The cause of this is still unknown. It is not known either what mechanism predisposes children with food allergy to develop asthma in later life. The majority of studies on "atopic march" are observational studies which evaluate the clinical course of the disease as well as the type of sensitization to food and inhaled allergens. Some studies evaluating these phenomena are based on the evaluation of bronchial reactivity, which sometimes does not correspond to the clinical manifestation of the disease and may remain latent [23]. In this work we decided to

find out whether there is any relationship between food allergy in infancy and a characteristic feature of asthma, i.e. bronchial hyperreactivity in a later period of life. It might be possible that food allergy in infancy will predispose to the development of bronchial hyperreactivity in a later period of life.

## Aim

Aim of the study was assessing bronchial hyperreactivity in school-age children with food allergy in infancy.

## Material and methods

This retrospective study included 158 children aged 7-18 years, who were diagnosed due to the suspicion of allergy in the Department of Allergology, Gastroenterology and Nutrition, Medical University of Lodz in the years 2008-2010. The study included children with atopic dermatitis, asthma or allergic rhinitis, whose parents reported food allergy in infancy, with the simultaneous introduction of an elimination diet for at least 6 months and improvement as a result of its use. Another prerequisite for inclusion in the study was the ability to undergo spirometry examination. Children with current food allergy were excluded from the study. A study group consisting of 52 children was created. The control group consisted of 60 children with corresponding disease entities, at the right age, without food allergy in the medical history. Finally 112 children were included in the experiment after receiving consent from the Bioethics Committee. The characteristics of the patients are presented in Table 1. The data of the studied population were gathered on the basis of a questionnaire survey, documentation and medical examination.

Skin-prick tests were carried out to assess sensitization to food and inhaled allergens. The tests were con-

**Table 1.** Patient characteristics

Parameters	Study group (N = 52)				Control group (N = 60)			
	Atopic dermatitis (N = 16)	Asthma (N = 21)	Allergic rhinitis (N = 15)	Total (N = 52)	Atopic dermatitis (N = 24)	Asthma (N = 19)	Allergic rhinitis (N = 17)	Total (N = 60)
Mean age (range) [years]	10.1 ±2.5 (7-18)	10.3 ±2.7 (7-18)	11.5 ±2.8 (8.9-18)	10.4 ±2.5 (7-18)	10.4 ±2.2 (7-18)	10.8 ±2.8 (7.5-17.7)	11.6 ±2.3 (8.3-18)	10.8 ±2.6 (8-18)
Boys, n (%)	8 (50)	12 (57.1)	7 (46.7)	27 (51.9)	13 (52)	13 (68.4)	7 (50)	33 (55)
Positive family history [%]	5 (31.2)	12 (57.1)	7 (46.6)	24 (46.1)	4 (16.6) <sup>a</sup>	11 (57.8)	6 (35.3)	21 (33.9)
tIgE [kU/l]	595 ±314 <sup>b</sup>	416 ±196	327 ±176 <sup>c</sup>	459 ±232	512 ±297	397 ±159	382 ±203	430 ±219
Passive smoking, n (%)	6 (35.3)	7 (33.3)	5 (33.3)	18 (34.6)	9 (37.5)	8 (42)	7 (41.2)	24 (40)
Breastfeeding ≥ 4 months, n (%)	9 (52.9)	14 (66.7)	7 (46.7)	30 (57.7)	11 (44.1)	8 (42)	7 (41.2)	26 (43.3)

<sup>a</sup>p < 0.05 (atopic dermatitis vs. asthma in the control group), <sup>b</sup>p < 0.05 (atopic dermatitis vs. asthma in the study group), <sup>c</sup>p < 0.05 (atopic dermatitis vs. allergic rhinitis in the study group)

ducted in compliance with the guidelines of EAACI [24]. Standardized extracts of food and inhaled allergens made by Allergopharma (Reinbek, Germany) were used. The following inhaled allergens were used: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, grass pollen (mix), mugwort, plantain, alder, hazel, birch, dog and cat dander, spores of *Alternaria* and *Cladosporium* and also food allergens: milk, egg, wheat flour, rye flour, cod fish, cocoa, hazelnut, walnut, peanut, citrus fruit, apple, strawberry, tomato, banana, celery, carrot, potato. The positive control was histamine (concentration 10 mg/ml) and the negative one was NaCl (0.9%). All the results in which the negative control caused a wheal  $\geq 3$  mm, the positive control was  $< 3$  mm and the difference between the diameter of the histamine wheal and the negative control was  $< 3$  mm were excluded. Erythema and wheal were measured and the arithmetic mean of the longest measurement of the erythema/wheal and the measurement which was perpendicular to it was noted [25]. The result was considered positive if the wheal diameter was bigger than for histamine and the reaction to histamine was greater than 3 mm.

Bronchial reactivity was evaluated with the methacholine provocation test (MP Biomedicals), using inhalant allergy Provocations System MES. The curve showing flow-volume values was the basis for evaluating initial parameters of FVC, FEV1, which in turn allowed for the assessment of the reaction to methacholine administered later. In nebulization PARI LC PLUS pressurized inhaler (capacity – 0.0054 ml/s) was used. The experiment was conducted in compliance with present standards, as recommended by ATS, using the Cockcroft method, starting with the concentration 0.03 mg/ml. The inhalation in free breathing with a clip on the nose lasted each time 2 min. The first solution administered during nebulization was buffered saline. Following that, methacholine solution in twofold increasing concentrations was applied in inhalation at intervals of 5 min. The provocation test was conducted as long as the medicine concentration in inhalation reached its maximum value or when FEV1 dropped by 20% in comparison to the initial value. The basis for the evaluation of the level of bronchial reactivity was provocation concentration PC20 mg/ml. Degree of bronchial reactivity was classified as: moderate hyperreactivity to severe hyperreactivity if PC20 was  $< 1$  mg/ml, mild if PC20 was between 1 mg/ml and 4 mg/ml, borderline hyperreactivity if PC20 was between 4 mg/ml and 16 mg/ml, normal reactivity if PC20 was  $\geq 16$  mg/ml [1, 26]. The criteria for exclusion from the methacholine provocation test were: obturation in initial spirometric and physical examination, pollen season in patients with seasonal allergy, the period following a respiratory system infection shorter than 6 weeks, asthma exacerbation, application of immunotherapy, the period following vaccination against influenza shorter than 3-6 weeks, the period following live virus vaccination shorter than

6 weeks. The experiment was carried out following contact with nicotine smoke (at least after 2 h), following the consumption of a caffeinated drink (at least after 6 h), following provocation with allergen (at least after 2 weeks), following the administering of  $\beta$ -mimetics and cholinolytics (at least after 12 h), following the administering of theophylline (at least after 48 h), following the administering of inhaled glucocorticosteroids (at least after 2 weeks if the patient had applied them chronically, with no time limitations), following the administering of antileukotriene drugs (at least after 24 h), following the administering of antihistamine drugs (at least after 2 weeks). Patients suffering from mucoviscidosis, musculoskeletal disorders, immune disorders, bronchopulmonary dysplasia, hypertension and epilepsy were excluded from the study.

### Statistical analysis

In the analyses the following tests were used:  $\chi^2$  test,  $\chi^2$  test with Yates' modification, Fisher's exact test, test for two means with small samples and Cochran-Cox test.

### Results

In the study group there were 16 children with atopic dermatitis, 21 with asthma and 15 with allergic rhinitis; in the control group there were respectively 24, 19 and 17 children (Table 1). The study and control groups did not differ in terms of the age and sex of the patients, although the children with allergic rhinitis were older than the children with atopic dermatitis and asthma. Allergic diseases in the family occurred in 24 children (46.1%) from the study group and in 21 children (33.9%) from the control group ( $p > 0.05$ ). A positive family history in children with asthma was significantly more frequent in children with asthma in comparison to children with atopic dermatitis in the control group ( $p = 0.01$ ). Such an observation was not noted in the study group. The mean total IgE concentration in the study group was  $459 \pm 232$  IU/ml and in the control group  $430 \pm 219$  IU/ml ( $p > 0.05$ ). Exposure to nicotine smoke referred to 18 children (34.6%) from the study group and 24 children (40%) from the control group ( $p > 0.05$ ). Breastfeeding exclusively for a period of at least 4 months occurred more often in children from the study group, i.e. in 30 children (57.7%), whereas in the control group it referred to 26 children (43.3%); the difference, however, was not statistically significant ( $p > 0.05$ ).

The mean value of FEV1 in the study group was  $95.7 \pm 8.8\%$  of the predictive values and it did not differ significantly from the corresponding value in the control group –  $95.9 \pm 9.8\%$  ( $p > 0.05$ ) (Table 2). Similarly, significant differences of mean FVC values in the study group ( $98.3 \pm 9.4\%$ ) and in the control group ( $98.9 \pm 7.8\%$ ) ( $p > 0.05$ ) were not observed.

A positive result of the provocation test with methacholine was obtained in 33 children (63.5%) from the study

**Table 2.** Results of provocation test with methacholine

	Study group (N = 52)				Control group (N = 60)			
	Atopic dermatitis (N = 16)	Asthma (N = 21)	Atopic dermatitis (N = 16)	Asthma (N = 21)	Atopic dermatitis (N = 16)	Asthma (N = 21)	Atopic dermatitis (N = 16)	Asthma (N = 21)
FEV1 (% predicted)	95.8 ±6.9	94.7 ±10.5	95.5 ±5.4	95.7 ±8.8	95.1 ±10.1	94.2 ±10.2	100.1 ±9.9	95.9 ±9.8
FVC (% predicted)	98.7 ±9.1	96.6 ±9.7	98.7 ±8.9	98.3 ±9.4	98.8 ±7.4	97.2 ±6.7	98.8 ±8.9	98.9 ±7.8
Positive provocation test with methacholine, n (%)	7 (43.7)	20 (95.2) <sup>a</sup>	6 (40) <sup>b</sup>	33 (63.5)	8 (33.3)	17 (89.5) <sup>c</sup>	5 (29.4) <sup>d</sup>	30 (50)
PC20 (mean ± SD) [mg/ml]	2.8 ±1.3	0.96 ±0.83 <sup>e</sup>	1.92 ±1.6 <sup>f</sup>	1.5 ±1.3	2.5 ±1.6	0.88 ±1.01 <sup>g</sup>	1.98 ±1.64 <sup>h</sup>	1.9 ±1.6

*ap* < 0.001 (atopic dermatitis vs. asthma in the study group), *bp* < 0.004 (asthma vs. allergic rhinitis in the study group), *cp* < 0.0007 (atopic dermatitis vs. asthma in the control group), *dp* < 0.003 (asthma vs. allergic rhinitis in the control group), *ep* < 0.0000 (atopic dermatitis vs. asthma in the study group), *fp* < 0.02 (asthma vs. allergic rhinitis in the study group), *gp* < 0.0004 (atopic dermatitis vs. asthma in the control group), *hp* < 0.01 (asthma vs allergic rhinitis in the control group)

group and in 30 children (50%) from the control group (Table 2) ( $p > 0.05$ ). Thus, bronchial hyperreactivity occurred more often in children from the study group than in children from the control group; the difference, however, was not statistically significant. A positive result of the provocation test with methacholine was obtained more often in children with asthma, atopic dermatitis, allergic rhinitis and food allergy in medical history in comparison to children with asthma, atopic dermatitis and allergic rhinitis but without food allergy in the medical history. Here, the difference was not statistically significant, either ( $p > 0.05$ ). Bronchial hyperreactivity occurred significantly more often in children with asthma (20, i.e. 95.2%) in comparison to children with atopic dermatitis (7, i.e. 43.7%) and also in comparison to children with allergic rhinitis (6, i.e. 40%) in the study group ( $p < 0.001$  and  $p < 0.004$  respectively). Similar differences were observed in the control group: bronchial hyperreactivity occurred significantly more often in children with asthma (17, i.e. 89.5%) in comparison to children with atopic dermatitis (8, i.e. 33.3%) as well as in comparison to children with allergic rhinitis (5, i.e. 29.4%) ( $p < 0.0007$  and  $p < 0.003$  respectively).

The level of bronchial hyperreactivity both in the study group and the control group was similar (Table 2). The mean level of PC20 in the study group was  $1.5 \pm 1.3$  mg/ml, and in the control group  $1.9 \pm 1.6$  mg/ml ( $p > 0.05$ ). The highest bronchial hyperreactivity was observed in children with asthma, both in the study group and in the control group – the value of PC20 was  $0.96 \pm 0.83$  mg/ml and  $0.88 \pm 1.01$  mg/ml respectively. PC20 levels were significantly lower in children with asthma in comparison to children with atopic dermatitis ( $2.8 \pm 1.3$  mg/ml) and those with allergic rhinitis ( $1.92 \pm 1.6$  mg/ml) in the study group ( $p < 0.0001$ ;  $p < 0.02$ ) as well as in the control group, where the corresponding levels were the following:  $2.5 \pm 1.6$  mg/ml;  $1.98 \pm 1.64$  mg/ml ( $p < 0.0004$ ;  $p < 0.01$ ).

Twenty-three children (44.2%) from the study group and 18 children (30%) from the control group ( $p > 0.05$ )

were sensitized to food allergens (Table 3). Most often positive results of skin prick tests with food allergens occurred in children with atopic dermatitis, both from the study group (9; 56.3%) and the control group (9; 37.5%). Sensitization to food allergens was observed more often in children with asthma and in children with allergic rhinitis from the study group in comparison to children with corresponding disease entities from the control group, although the differences were not statistically significant ( $p > 0.05$ ). Children from the study group were most often sensitized to fruit and vegetables, less often to nuts, milk, egg and flour. Children from the control group were most often sensitized to fruit, vegetables and nuts, less often to egg and flour; no child was sensitized to milk. Sensitization to inhaled allergens was similar in the two groups (in the study group 47, i.e. 90.4%, and in the control group 52, i.e. 86.7%). The most frequent was allergy to house dust mites: in the study group 32 children (68.1%) manifested this sensitization and in the control group 34 (65.4%). Sensitization to mites was followed by sensitization to pollen (26, i.e. 55.3%, in the study group and 27, i.e. 51.9%, in the control group).

## Discussion

The results of our studies showed that bronchial hyperreactivity in school-age children with atopic dermatitis or respiratory allergy and with food allergy in infancy occur more often than in children who have an analogous phenotype of the disease, but without food allergy in the history; however, the difference is not statistically significant. Moreover, it was proved that the degree of bronchial hyperreactivity in children with atopic dermatitis or respiratory allergy as well as with food allergy in infancy does not statistically differ in comparison to children with an analogous phenotype of the disease, but without food allergy in the medical history.

The results are an indirect proof that the increased bronchial reactivity in children from the study group is

**Table 3.** Sensitization to food and inhaled allergens in the study and control group

	Study group (N = 52)				Control group (N = 60)			
	Atopic dermatitis (N = 16)	Asthma (N = 21)	Atopic dermatitis (N = 16)	Asthma (N = 21)	Atopic dermatitis (N = 16)	Asthma (N = 21)	Atopic dermatitis (N = 16)	Asthma (N = 21)
<b>Sensitization to food allergens, n (%):</b>	9 (56.3)	9 (42.8)	5 (33.3)	23 (44.2)	9 (37.5)	5 (26.3)	4 (23.5)	18 (30)
<b>Milk</b>	3 (33.3)	1 (11.1)	1 (20)	5 (21.7) <sup>a</sup>	0	0	0	0
<b>Egg</b>	2 (22.2)	2 (22.2)	1 (20)	5 (21.7)	4 (44.4)	1 (20)	0	5 (27.7)
<b>Flour</b>	2 (22.2)	1 (11.1)	2 (40)	5 (21.7)	2 (22.2)	1 (20)	2 (50)	5 (27.7)
<b>Fish</b>	1 (11.1)	0	0	1 (4.3)	0	0	0	0
<b>Nuts</b>	4 (44.4)	2 (22.2)	2 (40)	8 (34.8)	5 (55.5)	1 (20)	2 (50)	8 (44.4)
<b>Fruit</b>	3 (33.3)	3 (33.3)	3 (60)	9 (39.1)	4 (44.4)	2 (40)	2 (50)	8 (44.4)
<b>Vegetables</b>	3 (33.3)	4 (44.4)	3 (60)	10 (43.4)	4 (44.4)	2 (40)	2 (50)	8 (44.4)
<b>Sensitization to inhaled allergens, n (%)</b>	11 (68.8) <sup>b</sup>	21 (100)	15 (100) <sup>c</sup>	47 (90.4)	16 (66.7) <sup>d</sup>	19 (100)	17 (100) <sup>e</sup>	52 (86.7)
<b>Mites</b>	8 (72.7)	16 (76.2)	8 (53.3)	32 (68.1)	11 (68.8)	14 (73.7)	9 (52.9) <sup>f</sup>	34 (65.4)
<b>Moulds</b>	2 (18.2)	4 (19)	2 (13.3)	8 (17)	4 (25)	5 (26.3)	3 (17.6)	12 (23.1)
<b>Pollen</b>	6 (54.5)	12 (57.1)	8 (53.3)	26 (55.3)	9 (56.2)	8 (42.1)	10 (58.8)	27 (51.9)
<b>Animal dander</b>	3 (27.2)	2 (9.5)	3 (20)	8 (17)	5 (31.2)	2 (10.5)	4 (23.5)	11 (21.2)

<sup>a</sup>*p* = 0.01 (study group vs. control group), <sup>b</sup>*p* = 0.01 (atopic dermatitis vs. asthma in the study group), <sup>c</sup>*p* = 0.03 (atopic dermatitis vs. allergic rhinitis in the study group), <sup>d</sup>*p* = 0.01 (atopic dermatitis vs. asthma in the control group), <sup>e</sup>*p* = 0.02 (atopic dermatitis vs. allergic rhinitis in the control group), <sup>f</sup>*p* = 0.04 (atopic dermatitis vs. allergic rhinitis in the control group)

connected with factors not related to food allergy in infancy. Prifits drew similar conclusions [27]. He stated that infants with egg and fish allergy manifest an increased risk of bronchial hyperreactivity in school age but at the same time he concluded that bronchial hyperreactivity was not related to atopic dermatitis in infancy, or persistent allergy to school age but it was related to early sensitization to inhaled allergens [27]. Experiments conducted so far have proved that sensitization to house dust allergens poses the most crucial factor in development of allergies of the respiratory system [28]. Besides, it was concluded that early exposure to high levels of house dust is a considerable risk factor for the development of asthma in people who are genetically predisposed [29]. Other findings show that in older children, who develop chronic asthma, the level of IgE in their 1<sup>st</sup> year of life is higher and such children are usually sensitized to inhaled allergens [30, 31].

In our studies, sensitization to house dust mites both in the study and control group was most frequent and at the same time comparable between these two groups. The lack of data from infancy made it impossible to assess the relationship between bronchial hyperreactivity and the onset of sensitization to house dust mites.

It is believed that bronchial hyperreactivity and atopic manifestation are important prognostic markers for devel-

opment of asthma in later life [32]. Results of studies prove that atopy increases the risk of bronchial hyperreactivity in the general population by 20-40% [33]. Although there is a close relationship between atopy and bronchial hyperreactivity, genetic predisposition to them seems to be independent [34]. Nelson concluded that the total number of positive skin-prick tests is related to the increased sensitization to methacholine [35]. According to epidemiological studies, mainly sensitization to allergens present in the house (cat and dog dander, dust mites) and then *Alternaria* contribute to higher bronchial hyperreactivity and increased risk of developing asthma [32]. It is also believed that the evaluation of skin sensitization is more helpful in prognosing the development of asthma and bronchial hyperreactivity than plasma total IgE concentration, although these two methods of assessing IgE-dependent allergy correlate with non-specific bronchial hyperreactivity [35-37]. In our studies, the level of tIgE, as well as the type and prevalence of sensitization to inhaled allergens did not differ between the study and the control group.

On the other hand, it was proved that the prevalence of bronchial hyperreactivity in patients with food allergy in the group sensitized to inhaled allergens is the same as in the group not sensitized, which might imply that sensitization to inhaled allergens is not the only factor

contributing to the development of bronchial hyperreactivity, connected with food allergy [13, 18].

A lot of studies indicate that children with food allergy manifest a higher risk of the development of bronchial hyperreactivity later in life [18]. In our study we observed higher, but statistically insignificant, prevalence of bronchial hyperreactivity in the group of children with food allergy in the history, in comparison to children without food allergy in the history.

Sensitization to food allergens in infancy has recently been included in the criteria of modified asthma predictive index (API) [38] but data on sensitization to food allergens in terms of the risk of developing asthma vary. According to the majority of current studies, food allergy in infancy increases the risk of bronchial hyperreactivity later in life but it is not dependent on sensitization to food allergens.

Unlike Prifit's studies [27], which concentrated on the history of natural allergy to egg and fish in children until school age, the MAS study (German Multicenter Allergy Study), including children up to the age of 5, showed that children who manifest persistent sensitization to food allergens, rather than those with transient sensitization or those not sensitized to food allergens at all, have a greater tendency to develop asthma or allergic rhinitis [39]. It should be emphasized that the same MAS cohort in the 7<sup>th</sup> year of life showed a three times higher risk of wheezing in children with early atopic dermatitis, irrespective of sensitization to egg or milk [40].

Among numerous common risk factors for the development of asthma, apart from atopy, exposure to nicotine smoke, prematurity, male sex, respiratory viral infections, abnormalities of the respiratory tract, allergic diseases in the family [41], and early exposure to allergens are often mentioned. Yet, data concerning this phenomenon are contradictory [42]. The results of recent studies show that there is not a linear dependence between early exposure to allergen and development of asthma, since exposure to both high and low amounts of allergen might be protective [43].

There are more and more controversies regarding the most effective methods of preventing allergic diseases. However, on the basis of a meta-analysis comprising 3271 children it was concluded that in children with an increased risk of developing asthma, various methods, including avoiding allergens in the diet as well as eliminating certain environmental factors, result in a decrease in asthma prevalence later in childhood by 50% [44].

Exposure to both food and inhaled allergens plays an important role in the development of allergic diseases. It was proved that apart from the relationship with asthma, atopy, and infections of the respiratory system [45], bronchial hyperreactivity is connected with exposure to food allergens [46-48]. Long-term studies on the time of introducing solid food into an infant's diet, no matter whether he/she is in the risk group, showed that intro-

ducing allergy-inducing foods later than normal does not decrease the risk of developing asthma. This observation was one of the reason for the change in dietary recommendations for infants [49]. Although in our study the mean time of introducing solid foods into an infant's diet in the group without food allergy in the history concerned younger children than in the case of children with food allergy in the history, the differences were not significant. It might have resulted from "intentional" late introduction of solid foods into an infant's diet, especially in children who belonged to the risk group. Also, the prevalence of allergic diseases in the family, both in the study and control group, was similar.

The average time of exclusive breastfeeding in the group of children with food allergy in the history was longer in the control group but the difference was not statistically significant. When we take into consideration the fact that bronchial hyperreactivity occurred more often in children with food allergy in the history, who were also breastfed longer, we can conclude that longer breastfeeding contributes to bronchial hyperreactivity. We should however remember that we observe here a so-called inverse causal relationship; it means that mothers of children suffering from allergic diseases usually breast-feed them longer with the aim of prevention. The relation between the protective effect of breastfeeding and the risk of developing asthma remains controversial. A meta-analysis of 12 prospective studies on children exclusively breastfed for a period of at least 3 months proved the protective effect of breastfeeding on the risk of asthma development in children with a positive family history (OR = 0.52). In children belonging to the general population the effect was weaker (OR = 0.7) and in children without atopy or allergic diseases it was insignificant (OR = 0.99) [50]. Moreover, a study of 1200 unselected newborns showed that the relationship between breastfeeding and asthma is modified by the presence of asthma in the mother, age and the presence of atopy in the child. The protective effect appears only in the early period of life [51]. The KOALA cohort study showed that the longer breastfeeding is, the lower the risk of atopic dermatitis in children of mothers without allergy/asthma. For mothers with asthma there is no relationship between the time of breastfeeding and the development of atopic dermatitis in infancy. Longer breastfeeding decreased the risk of wheezing in the first 2 years of life, independently of atopy in the mother. It is suggested that the protective effect of breastfeeding on recurrent wheezing might be connected with the prevention of infections of the respiratory system [52]. The relationship between breastfeeding, wheezing, lung function and atopy was analysed in the International Study of Asthma and Allergy in Childhood (ISAAC) phase II. It was concluded that there is a protective effect of breastfeeding on non-atopic wheezing [53]. Such an effect was not related to the risk of development of allergic diseases later in life [54].

It is worth mentioning that although bronchial hyperreactivity is a pathognomonic feature of asthma, van den Nieuwenhof states that the evaluation of asymptomatic bronchial hyperreactivity does not identify patients with an increased risk of asthma development but allergy does [55]. Epidemiological analyses show that the prevalence of asymptomatic bronchial hyperreactivity in the general population is 7-16% [56-58]. There are suggestions that 14-58% of people with asymptomatic bronchial hyperreactivity develop asthma [59]. Asymptomatic bronchial hyperreactivity was observed in 8-13% of children from the general population [57, 58], in 28-61% of children with allergic rhinitis [60] and in 30-81% of children with atopic dermatitis [61, 62]. Asymptomatic bronchial hyperreactivity in the study group was observed more often than in the control group in children with atopic dermatitis (43% and 33% respectively) and in children with allergic rhinitis (49% and 29% respectively). The results of our studies are comparable to those conducted by other authors. No significant differences were noted for food allergy in the history.

In our study another risk factor for development of bronchial hyperreactivity was also considered. It was exposure to nicotine smoke [63]. The data in the study group and in the control group were similar. It can thus be concluded that exposure to nicotine smoke did not have any influence on prevalence or intensity of bronchial hyperreactivity.

Bearing in mind the proved dependence of bronchial hyperreactivity on age and sex [64], the study and control groups were selected in such a way that those elements could not affect the experiment findings.

The retrospective nature of the study is a limitation. Therefore a possibility of fault is always probable. The study does not have detailed data on the infancy period and it is based to a great extent on the data gathered in the medical history. However, upon the conducted analysis and review of the literature it is seemed that the study on the relationship between bronchial hyperreactivity and factors which might modify it, including exposure to food allergens, remains an open problem. The opinion that food allergy might lead to bronchial hyperreactivity is still controversial and requires further studies. The question whether a diet devoid of food allergens in early childhood protects the child against inhaled allergy later in life has not been answered yet.

## Conclusions

1. Prevalence and degree of bronchial hyperreactivity in school children with atopic dermatitis, asthma, allergic rhinitis and food allergy in infancy do not differ significantly from those in children having a corresponding disease phenotype, without food allergy in the history.
2. Bronchial hyperreactivity in school-age children with allergic diseases does not show a relationship with food allergy in infancy.

3. Sensitization to food allergens occur more often in school children with atopic dermatitis, asthma, allergic rhinitis and food allergy in the history, in comparison to children with corresponding disease phenotype, but without food allergy in infancy; however, the difference is not statistically significant.

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