

The prevalence of allergic diseases in an unselected group of 6-year-old children. The DARC birth cohort study

Kjaer HF, Eller E, Høst A, Andersen KE, Bindslev-Jensen C. The prevalence of allergic diseases in an unselected group of 6-year-old children. The DARC birth cohort study. *Pediatr Allergy Immunol* 2008.

© 2008 The Authors

Journal compilation © 2008 Blackwell Munksgaard

This study determines the prevalence of atopic dermatitis, asthma, rhinoconjunctivitis, food hypersensitivity and urticaria and the frequency of sensitization in children with and without clinical allergic disease. In an ongoing prospective non-interventional birth cohort study of 562 unselected children, 404 children were subjected to interview, clinical examination, lung function measurements and allergy testing at 6 yr of age. Sensitization measured by skin prick test (SPT) and specific immunoglobulin E (S-IgE) was determined for 24 different allergens. The 1-yr period prevalence of atopic dermatitis, asthma and rhinoconjunctivitis was 14.4%, 6.2% and 13.6%. 25.7% of the children suffered from at least one of the three diseases. The frequency of sensitization in children with no disease (controls), any allergic disease, atopic dermatitis, asthma and rhinoconjunctivitis was 17%, 45%, 47%, 56% and 55% (defined as SPT ≥ 3 mm and/or S-IgE ≥ 0.35 kU/l for at least one allergen). Symptoms were linked to sensitization for 44% in the asthma group and 42% in the rhinoconjunctivitis group, whereas sensitization could not be linked to worsening of the eczema in any cases of atopic dermatitis. Overlap between the three diseases was significantly more frequent in sensitized children than in non-sensitized (19/46 = 41% vs. 9/58 = 16%, $p = 0.004$). The prevalence of food hypersensitivity and urticaria was 1.2% and 5.4% respectively. In unselected 6 yr old children, approximately half of the children with atopic dermatitis, asthma or rhinoconjunctivitis are IgE-sensitized. Sensitization tends to link these diseases to each other.

Henrik Fomsgaard Kjaer¹, Esben Eller¹, Arne Høst², Klaus Ejner Andersen¹ and Carsten Bindslev-Jensen¹

Departments of ¹Dermatology and ²Pediatrics, Odense University Hospital, University of Southern Denmark, Odense, Denmark

Key words: prevalence; atopic dermatitis; asthma; rhinoconjunctivitis; sensitization; birth cohort; food hypersensitivity; urticaria

Henrik Fomsgaard Kjaer, Allergy Centre,
Department of Dermatology,
Odense University Hospital, 29 Sdr. Boulevard,
5000 Odense C, Denmark
Tel.: +45 65412717
Fax: +45 63121507
E-mail:
henrik.fomsgaard.kjaer@ouh.regionsyddanmark.dk

Accepted 25 January 2008

Longitudinal prospective birth cohort investigations of children encompassing frequent interviews by doctors, clinical examinations and tests for sensitization are few (1) but much required in order to describe the natural history of allergic diseases and sensitization. A detailed description of an unselected cohort facilitates the transferability of the results to the general population. The DARC birth cohort study follows prospectively a cohort of unselected children from birth into adulthood. Earlier results from the cohort

have been published. The prevalence of allergic diseases and sensitization in the cohort from 0–18 months of age have been thoroughly described (2–5), while the follow up at 36 months focused on food allergy (6, 7). As the first step for coming longitudinal analysis, this paper reports prevalence measures of atopic dermatitis, asthma, rhinoconjunctivitis, food hypersensitivity and urticaria in our cohort of children at 6 yr of age, and describes the pattern of sensitization in children with and without allergic disease.

Materials and methods

Study design

In 1998/99, the Danish Allergy Research Centre (DARC) launched a prospective non-interventional birth cohort study with the aim of describing the prevalences and risk factors of sensitization and allergic diseases in childhood. A detailed description of the establishment of the cohort and the mode of selection has been published (3). In brief, 997 children were offered participation according to the inclusion and exclusion criteria, 435 declined, leaving 562 children for future follow-up examinations. These 562 children did not differ significantly from those who declined participation regarding gender, mother's age, birth weight, parity, gestational age or Apgar scores. The final cohort had 51% boys and 49% girls. The study protocol was approved by the local ethics committee (ID 19980102).

The children were examined at 0, 3, 6, 9, 12, 18, 36 and 72 months of age. All visits included an extensive questionnaire-based interview (regarding atopic heredity, medical history and environmental factors), clinical examination by a doctor, and (except at 9 months) skin prick testing (SPT) and immunoglobulin E (IgE) measurements. At 72 months lung function measurements were added. In case of no show, the interview was made by telephone.

The 6-yr follow-up examination at the clinic was completed by 404/562 children (72.0%). Another 57 children were interviewed by telephone, but as these children could not be submitted to important aspects of the diagnostic work up and tests for sensitization, they were excluded from further analysis. The analysed subsample of the 404 children did not differ significantly from the original cohort of 562 children with respect to gender, parental social class, mother's age, birth weight, parity or parental smoking habits during pregnancy or at time of birth. Allergic pre-disposition (no, single or double) was present in 53.6%, 37.9% and 8.5% among the 562 children originally included and 53.5%, 37.9% and 8.7% in the 404 children examined at 6 yr of age. The study population of 404 children was very homogeneous regarding anthropometric data; median age was 6.1 yr (s.d. 0.15 yr), median height 119 cm (s.d. 5 cm) and weight 22.1 kg (s.d. 3 kg).

Diagnostic work up

Skin prick test. Skin prick test was performed according to the European Academy of Aller-

gology and Clinical Immunology (EAACI) guidelines (6, 8, 9). The children were tested with 11 inhalant allergens (commercial allergen extracts, ALK-ABELLÓ, Copenhagen, Denmark) and 10 food allergens by prick to prick technique with fresh food (10). Allergens tested are presented in Table 1.

IgE measurements. Specific IgE (S-IgE) was measured by ImmunoCap (Phadia, Uppsala, Sweden) for the same allergens as used for SPT, and in addition cockroach and the moulds *Penicillium notatum* and *Aspergillus fumigatus* (Table 1).

Table 1. Sensitization to different allergens in children with atopic dermatitis, asthma, rhinoconjunctivitis or any disease

	Atopic dermatitis	Asthma	Rhinoconjunctivitis	Any disease*
Total	58	25	55	104
SPT performed†	55 (+2)	24 (+1)	52 (+2)	100 (+2)
S-IgE performed	54	24	51	96
SPT/S-IgE performed	57	25	55	103
Sensitized by SPT	21	12	25	34
Sensitized by S-IgE	25	14	28	43
Sensitized by either SPT or S-IgE	27 (47%)	14 (56%)	30 (55%)	46 (45%)
Not sensitized	30	11	25	57
Relevant sensitization	0	11	23	25
Birch	8/11/11	4/5/5	9/14/15	11/16/17
Grass	12/12/13	4/5/5	14/14/15	17/19/20
Mugwort	3/5/6	1/0/1	4/6/7	4/7/8
Horse	3/3/4	4/3/4	5/6/8	5/6/8
Dog	8/10/11	8/9/9	9/12/13	11/15/17
Cat	5/7/7	5/6/6	6/10/10	7/11/11
Dermatophagoides pteronyssinus d1	9/10/10	9/10/10	9/13/13	12/16/16
Dermatophagoides farinae d2	8/12/12	8/10/10	9/14/14	12/19/19
Moulds‡	0/6/6	0/4/4	1/9/9	1/10/10
Latex	0/3/3	0/0/0	1/4/4	1/5/5
Cockroach	-1/1	-1/1	-1/1	-2/2
Cow's milk	1/6/6	1/4/4	1/7/7	1/10/10
Hen's egg	4/10/11	3/6/7	3/8/9	6/16/18
Wheat	1/3/3	0/3/3	2/5/5	2/7/7
Peanut	1/3/3	1/2/2	1/5/5	1/6/6
Soy	1/3/3	0/2/2	2/5/5	2/6/6
Hazelnut	3/3/4	1/1/2	3/4/6	4/5/7
Celery	0/1/1	0/0/0	1/3/3	1/3/3
Brazilnut	1/1/1	1/1/1	1/2/2	1/2/2
Shrimp	0/0/0	0/0/0	0/0/0	0/0/0
Codfish	0/1/1	0/0/0	0/1/1	0/1/1

Sensitization to allergens is expressed as SPTpositive/S-IgEpositive/SPT and/or S-IgEpositive.

*Atopic dermatitis, asthma, rhinoconjunctivitis or any combination of these. This column is not the sum of the three other columns because of overlap between the diseases.

†Numbers in brackets denotes children only partially skin prick tested.

‡*Alternaria alternata*, *Cladosporium herbarum*, *Penicillium notatum* (only S-IgE) and *Aspergillus fumigatus* (only S-IgE).

Lung function measurements. Spirometry was attempted in all children examined at the clinic, but a detailed description of the results is beyond the scope of this manuscript. Lung function was measured by dynamic spirometry using the MicroLoop equipment and the corresponding SPIDA Software V 5.0 including an animation program (Micro Medical Ltd, Rochester, UK). All measurements were carried out by the same investigator. Children were at rest for at least 15 min before spirometry. Age was recorded and height and weight were measured. Each child was instructed thoroughly to blow as hard, fast and for as long time as possible into the mouthpiece and practiced on the mouthpiece alone under supervision until the technique was acceptable. Individual flow-volume curves were then made with the child standing wearing a nose clip. Three acceptable flow-volume curves were recorded whenever possible. Individual curves were reviewed and accepted if: (i) The flow-volume curve had a rapid rise to peak flow and a gradual flow decrease with no signs of abrupt end (sharp drop of flow) or evidence of cough or glottic closure. A distinct peak (and one only) was mandatory, (ii) the American Thoracic Society start of test criteria were fulfilled (11), (iii) the volume-time trace was approaching a horizontal plateau, (iv) the duration of expiration was ≥ 1 s. At least two acceptable flow-volume curves were achieved by 368/404 children (91%). In addition to baseline spirometry, children with wheeze, coughing episodes, shortness of breath or reduced physical activity within the last year and children with known asthma performed a bronchodilator test 15 min after inhalation of NES-spacer Bricanyl® (AstraZeneca), 0.25 mg/dose $\times$ 4. A bronchodilator test was positive when $\Delta FEV_1 \geq 12\%$. When necessary for the diagnosis, an exercise test was performed after the baseline testing (free running with maximum effort for 6 min and then spirometric testing 5 and 10 min after). An exercise test was regarded positive if the decrease in $FEV_1 \geq 12\%$. A bronchodilator test was performed in 50 children with symptoms and an exercise test was performed in 14 children.

Oral food challenges. Whenever food hypersensitivity was suspected (see below) a double-blind placebo controlled food challenge (DBPCFC) was performed according to EAACI guidelines (12). In case of non-cooperation or decline of DBPCFC, an open-controlled food challenge (OCFC) was performed.

Definitions and diagnostic criteria

Sensitization. A positive SPT was defined as a wheal size of ≥ 3 mm larger than the negative control. Specific IgE was classified as positive if ≥ 0.35 kU/l.

Clinical relevance. Sensitization was regarded clinically relevant if there was a clear connection between the symptoms described (suspected allergen) and the result of the SPT/S-IgE. The term clinical irrelevant sensitization is used when exposure to the allergen, does not result in clinical symptoms or worsening of already present symptoms.

Allergic pre-disposition. Allergic pre-disposition was defined as a doctor's diagnosis of atopic dermatitis, asthma, rhinoconjunctivitis or food allergy in one or both parents at any time.

Atopic dermatitis. The diagnosis of atopic dermatitis was based on the Hanifin-Rajka criteria, requiring the presence of at least three of four basic features and at least three of 23 minor features (13). Of 23 minor features, four were excluded: keratoconus and anterior subcapsular cataract (as they required an ophthalmologist), early age of onset (because of age of study population) and white dermographism/delayed blanch. Fulfilment of a given feature was evaluated from both the questionnaire and the clinical examination.

Asthma. Asthma was diagnosed if one of the following criteria was fulfilled: (i) recurrence of at least two of the three symptoms cough, wheeze and shortness of breath within the previous 12 months (symptoms not triggered only by infections) (14), (ii) doctors' diagnosis of asthma prior to follow-up visit (in combination with ongoing treatment), (iii) symptoms suggestive of asthma within the previous 12 months in combination with a positive exercise or bronchodilator test. Symptoms suggestive of asthma was isolated persistent cough, wheeze or shortness of breath (apart from colds), exercise induced symptoms or reduced physical activity. For all three criteria, a clear subjective or objective response to treatment with β_2 -agonists and/or inhaled corticosteroids was demanded for the diagnosis of asthma.

Rhinoconjunctivitis. Rhinoconjunctivitis was diagnosed in children with recurrence (at least two separate episodes) of one or more typical symptoms from eyes and/or nose (not related to common colds) according to the standardized questionnaire. Typical symptoms were nasal

pruritus, runny nose, sneezing spells, nasal stenosis/mouth breathing, itchy eyes, conjunctival injection or watery secretion from both eyes. Rhinoconjunctivitis was used as an umbrella term for children with conjunctivitis, rhinitis or both conditions, but prevalence measures for all three conditions are outlined.

Food hypersensitivity. Food hypersensitivity was defined as a positive food challenge (DBPCFC or OCFC) according to EAACI guidelines (12). Oral food challenge was performed if: (i) the parents reported of any adverse reactions of the child to food items, (ii) SPT and/or S-IgE was positive to a given food item and there was no 'clear-cut negative history' of the child eating that particular item without adverse reactions or (iii) a prior DBPCFC/OCFC positive to a given food item, had not been followed by a negative challenge or 'a clear-cut negative history'.

Urticaria. Urticaria was diagnosed, if a confirmatory answer to the following question was given: 'Did your child during the last year experience a fleeting skin rash characterized by wheals (central swellings) surrounded by erythema and with associated itching?'

Statistics. All data were entered into a Microsoft Access Database. Every tenth dataset was entered twice. Any discrepancy was corrected manually. All statistical analyses were performed with STATA 9.1 (Stata Corporation, College Station, TX, USA). Fisher's exact test (two-sided) was used for comparison of frequencies between groups and 95% confidence intervals were estimated.

Results

A total of 404 children were examined, 204 girls (50.5%) and 200 boys (49.5%). SPT was performed in 384/404 = 95.0% (195 girls and 189 boys). A positive SPT was more frequent in boys than in girls (35/189 = 18.5% vs. 19/195 = 9.7%, $p = 0.018$), because of a difference in sensitization to inhalant allergens (SPT positive in 33/189 = 17.5% boys vs. 17/195 = 8.7% girls, $p = 0.015$), whereas a positive SPT towards a food allergen was equally distributed (7/189 = 3.7% vs. 7/195 = 3.6%). Specific IgE was measured in 351/404 children = 86.9% (179 girls and 172 boys). A positive S-IgE was found in 49/172 = 28.5% of the boys and 40/179 = 22.3% of the girls ($p = 0.220$). Sensitization to inhalant allergens by S-IgE differed between genders (38/172 = 22.1% in boys vs. 22/179 = 12.3% in girls, $p = 0.016$ for difference), whereas S-IgE for at least one food allergen was observed in 25/172 = 14.5% boys and 28/179 = 15.6% girls.

A diagnosis of atopic dermatitis, asthma, rhinoconjunctivitis or a combination of these diseases (allergic disease) was given to 104/404 children (25.7%), 300/404 children (74.3%) were classified as healthy. Included in the healthy group was one child with food allergy and an episode of urticaria because of egg (sensitized to egg and milk only) and 10 children with an acute episode of urticaria within the last year not related to allergy (three were monosensitized but with no connection between the allergen and urticaria). Sensitization to at least one allergen was significantly more frequent in children with allergic disease as opposed to healthy children ($p < 0.001$ for SPT, S-IgE and SPT and/or S-IgE) (Fig. 1). The 12-month period prevalence for atopic dermatitis was 58/404 = 14.4% (11.3–18.1%), for asthma 25/404 = 6.2% (4.2–9.0%) and for rhinoconjunctivitis 55/404 = 13.6% (10.6–17.3%). Sensitization to at least one allergen by SPT, S-IgE and SPT/S-IgE was present in approximately half of the children in each of the three groups (Fig. 2). Table 1 specifies sensitiza-

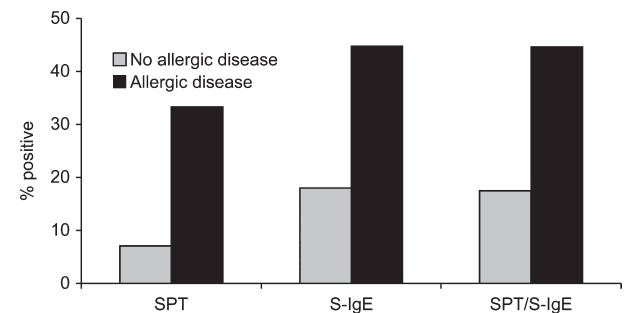


Fig. 1. The frequency of sensitization (to at least one allergen) by SPT, S-IgE and SPT and/or S-IgE in 6-year-old children with (n = 104) and without (n = 300) allergic disease.

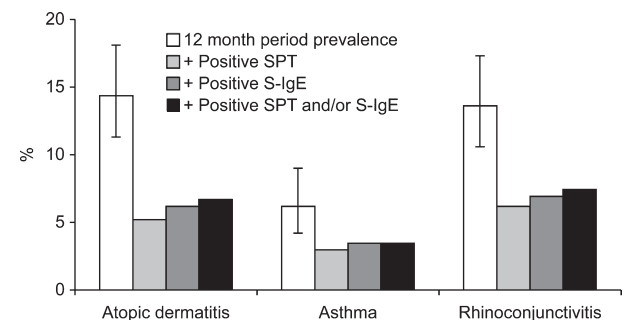


Fig. 2. 12 month period prevalences (with 95% CI intervals) for atopic dermatitis, asthma and rhinoconjunctivitis - and frequency of sensitization (to at least one allergen) in the different disease groups as measured by SPT, S-IgE, and SPT and/or S-IgE.

tion by SPT, S-IgE and SPT/S-IgE in the three disease groups to individual allergens and will be discussed in the following along with the relevant type of allergic disease.

Out of 104 children with atopic dermatitis, asthma or rhinoconjunctivitis, 76 children (73%) were diagnosed with one of the three diseases, 22 (21%) with two of the three diseases and six children (6%) with all three diseases (Fig. 3a). Separation of these children into sensitized (Fig. 3b) and not sensitized (Fig. 3c) demonstrated that children with more than one of the three diseases were significantly more frequent in the sensitized group ($19/46 = 41\%$ vs. $9/58 = 16\%$, $p = 0.004$). The frequency and type of sensitization was dependent on the type and especially the combination of the three allergic phenotypes as discussed in the following (Table 2).

At 6-yr of age, 21% (45/216) of the children with no allergic pre-disposition, had a diagnosis of atopic dermatitis, asthma or rhinoconjunctivitis, the number being 29% (45/153) in children with single parental pre-disposition and 40% (14/35) in children with double parental pre-disposition. In children with no allergic pre-disposition ($n = 216$), 24, 10 and 27 were diagnosed with atopic dermatitis, asthma or rhinoconjunctivitis, respectively. In children with single pre-disposition ($n = 153$), these numbers were 25, 14 and 20 and for children with double parental pre-disposition ($n = 35$), 9, 1 and 8.

Atopic dermatitis

In 58 children diagnosed with atopic dermatitis, 27/57 (47%) were sensitized in either SPT and/or S-IgE. The children with atopic dermatitis were

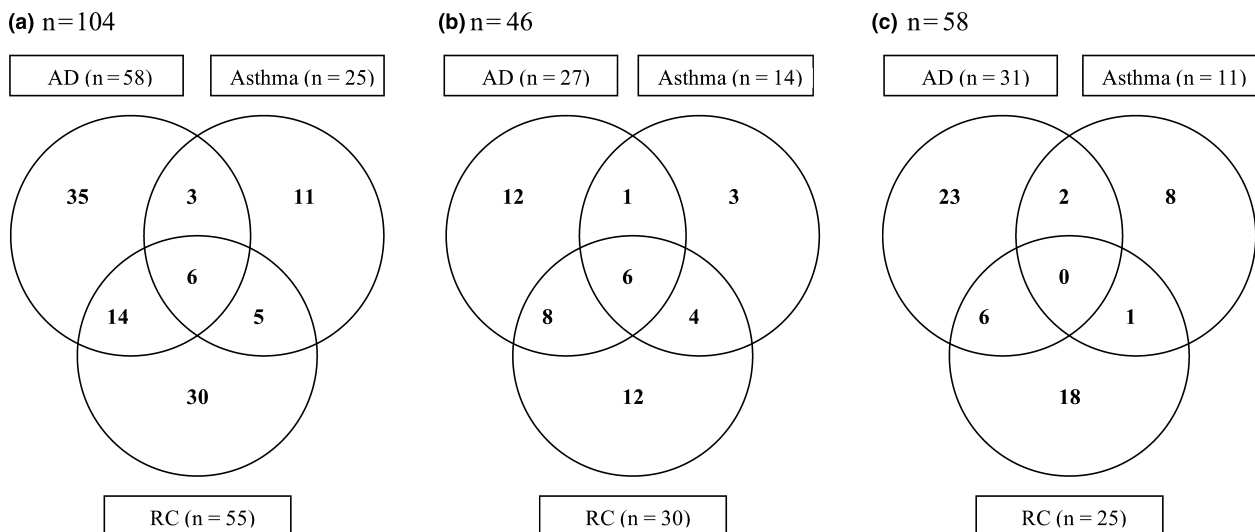


Fig. 3. Overlap between children with atopic dermatitis, asthma and rhinoconjunctivitis in all children with allergic disease (a) and subdivided into sensitized (b) and not sensitized children (c). AD, atopic dermatitis; RC, rhinoconjunctivitis.

Table 2. The frequency of sensitization in children with different combinations of allergic disease (and no allergic disease)

	AD alone	AB alone	RC alone	AD+AB	AD+RC	AB+RC	AD+AB+RC	AD/AB/RC	None
Total	35	11	30	3	14	5	6	104	300
SPT performed*	34	11	29	3	13 (+1)	5	5 (+1)	100 (+2)	273 (+9)
S-IgE performed	32	10	27	3	13	5	6	96	255
SPT or S-IgE performed	34	11	30	3	14	5	6	103	286
Sensitized (SPT and/or S-IgE)	12 (35%)	3 (27%)	12 (40%)	1 (33%)	8 (57%)	4 (80%)	6 (100%)	46 (45%)	50 (17%)
Not sensitized	22	8	18	2	6	1	0	57	236
Pollen	4/5/5	0/1/1	6/7/8	0/0/0	7/6/7	1/1/1	5/5/5	23/25/27	11/12/15
Pets	1/1/2	0/1/1	3/4/6	1/1/1	2/3/3	2/2/2	5/5/5	14/17/20	2/2/2
Mites	1/3/3	1/1/1	1/4/4	1/1/1	2/2/2	2/2/2	5/6/6	13/19/19	7/13/13
Moulds†	0/0/0	0/0/0	1/4/4	0/1/1	0/2/2	0/0/0	0/3/3	1/10/10	0/2/2
Foods	3/6/6	0/3/3	2/4/5	0/0/0	1/3/3	2/2/2	3/5/5	11/23/24	3/30/30

Sensitization to different allergen groups is expressed as SPTpositive/S-IgEpositive/SPT- or S-IgEpositive.

AD, atopic dermatitis; AB, asthma; RC, rhinoconjunctivitis; None, no allergic disease.

*Numbers in brackets denotes children only partially skin prick tested.

†*Alternaria alternata*, *Cladosporium herbarum*, *Penicillium notatum* (only S-IgE) and *Aspergillus fumigatus* (only S-IgE).

most frequently sensitized to grass pollen (13/57 = 23%), *dermatophagoides farinae* (21%), birch and dog (19%) among inhalant allergens, and hen's egg (19%) among food allergens (Table 1). In the group with atopic dermatitis alone, the degree of sensitization was lower (12/34 = 35%) (Table 2) than in the group of all children with atopic dermatitis, which was also true for all individual allergens. In the group of children with atopic dermatitis, 34% were also given a diagnosis of rhinoconjunctivitis and 16% a diagnosis of asthma (Fig. 3a), these numbers being 52% and 26% in children with atopic dermatitis and sensitization (Fig. 3b).

Asthma

Criterion 1 for asthma was fulfilled by 13 children, criterion 2 by six children and criterion 3 by another six children. A total of 14/25 (56%) children diagnosed with asthma were sensitized by either SPT and/or S-IgE. Clinical relevant sensitization was present for 11/14 sensitized children. Sensitization occurred most often to the two house dust mites (10/25 = 40%) and dog (36%) among inhalant allergens (Table 1). The frequency of sensitization was low in the group of asthma alone (3/11 = 27%) (Table 2). In the group of children with asthma, 44% were given a diagnosis of rhinoconjunctivitis and 36% a diagnosis of atopic dermatitis (Fig. 3a), in sensitized children with asthma these numbers were 71% and 50% (Fig. 3b).

Rhinoconjunctivitis

In children diagnosed with rhinoconjunctivitis, 37/55 (67%) were noticed to have symptoms from both eyes and nose, 12/55 (22%) only from the eyes and 6/55 (11%) only from the nose. Sensitization was present in 30/55 children (55%) by either SPT and/or S-IgE, and clinically relevant in 23/30 sensitized children. The 12-month period prevalence for clinical relevant allergic rhinoconjunctivitis was in that respect 23/404 = 5.7% (3.8–8.4%). Sensitization occurred most often to grass and birch (15/55 = 27%), house dust mites (13/55 = 24% and 14/55 = 25%) and dog (13/55 = 24%) (Table 1). A relevant connection between symptoms and sensitization was only present for pollen, pets and dust mites. Specific suspicion to pollen-related rhinoconjunctivitis was stated by the parents of 19 symptomatic children and sensitization to pollen confirmed for 10 of these children (53%). In the group of children with rhinoconjunctivitis alone, the degree of sensi-

zation was lower (than for all children with rhinoconjunctivitis) as 12/30 = 40% were sensitized, not surprisingly grass and birch were still the predominant allergens (Table 2). Sensitization to food allergens was common in children with rhinoconjunctivitis (Table 1), but apart from one peanut allergic patient and a few children with oral allergy syndrome (15), the sensitizations were serological, clinically irrelevant cross reactions. In the group of children with rhinoconjunctivitis, 20% also had a diagnosis of asthma and 36% of atopic dermatitis (Fig. 3a); in children with rhinoconjunctivitis and sensitization, these numbers were 33% and 47% (Fig. 3b).

Food hypersensitivity

According to the definitions described, 13 children were eligible for food challenge and a total of five DBPCFCs and eight OCFCs were performed. Food challenges were performed with hen's egg (9), peanut (2), cow's milk (1) and shrimp (1). The food challenge was positive for five children, the prevalence of food hypersensitivity being 5/404 = 1.2% (0.4–3.0%). Food hypersensitivity was restricted to two allergens, three children reacted to hen's egg and 2 children towards peanuts.

Urticaria

The parents of 22 children [5.4% (3.6–8.2%)] stated that their child had experienced urticaria within the previous 12 months. As a few children had more than one episode, a total of 26 cases of acute urticaria were recorded; 13 were doctors diagnosed and 13 diagnosed by the parents. Eliciting factors (equally distributed in the two groups) constituted unknown cause (54%), contact urticaria caused by furred animals (23%), infection (15%) and ingestion of hen's egg (8%).

Discussion

The term unselected study population should not be used without carefully considering possible selection bias. The follow-up rate at this examination was high and no significant differences between the analysed subsample and the original cohort were found (nor between the cohort and those declining participation in the study), advocating for the representativeness of our prevalence measures. Selection bias regarding the analysis of sensitization seems negligible given the high proportion of children tested (only 15 children were not tested by at least one method).

The participation in a cohort study results in increased awareness regarding allergic diseases and the families in the study presumably tended to avoid possible risk factors more often than the general population, indicating a possible underestimation of our prevalences. On the other hand, among children lost to follow up, there might be a predominance of healthy children, leading to an overestimation of the prevalences. Possibly parents with allergic disease themselves might be more prone to accept study participation, but the prevalence of a positive skin prick test in mothers (20.2%) and fathers (32.6%) of children in the final cohort (91% tested at baseline) were not higher than in a large unselected Danish adult population (16). In conclusion, we consider the transferability of our results to the general population to be very high.

The 12-month period prevalence of atopic dermatitis at 6 yr of age was 14.4% (11.3–18.1%). However, the usefulness of the Hanifin–Rajka criteria in population-based studies can be questioned. The original paper by Hanifin and Rajka (13) provides a breeding ground for different interpretations of the criteria and especially in children the significance of the minor signs is doubtful (17). Obstacles appear in trying to compare our prevalence measures with other studies. Some studies do not differentiate sufficiently between epidemiological frequency measures, others use different diagnostic criteria or report prevalences for other age groups. The ISAAC Study assessed prevalence measures for atopic dermatitis through questions corresponding closely to the major criteria proposed by Hanifin and Rajka. A recent paper from ISAAC Phase Three confirmed not only the well-known large differences across the world in the prevalence of atopic dermatitis, but highlighted that these prevalences were increasing in most centres in the 6–7 yr age group (18). Countries normally comparable with Denmark showed a marked difference in 12-month period prevalence from 7.9% in Germany to 22.9% in Sweden for the 6–7 yr age group. Previous frequency measures of atopic dermatitis in this age group in Denmark are not easily comparable with our figures, but Schultz-Larsen (19) reported a lifetime-prevalence for 7-yr-old children of 22.9% in 1992 and Olesen et al. (20) a cumulative incidence in 7-yr-old children in 1993 and 1998 of 18.9% and 19.6%, respectively.

How atopic is atopic dermatitis? Our data demonstrated that 47% of children with atopic dermatitis at 6 yr of age were IgE-sensitized, which is in reasonable agreement with other

studies of pre-school children (21, 22). Sensitization was more frequent among children with atopic dermatitis than in the group of healthy children, but in no cases of atopic dermatitis could sensitization at 6 yr of age be demonstrated to be of any clinical relevance for the eczema. The group of children with atopic dermatitis included three children with proven food hypersensitivity, but in none of the three cases ingestion of the food in question could be confirmed to cause worsening of the eczema. As these children only ingested the food item they were allergic to in connection to oral food challenge or by accident, the possible link between ingestion and worsening of the eczema was not completely clarified. Sensitization in children with atopic dermatitis in this age group seems of little relevance in relation to their eczema, but is important in terms of co-existing or future development of allergic respiratory disease.

Unfortunately, no generally accepted criteria for asthma in epidemiological studies are available, and especially in children the case definition can be difficult as symptoms of the disease are heterogeneous. The task of choosing a set of diagnostic criteria for asthma in a study might put the investigator in a dilemma, whether to go for simple criteria used also in other studies facilitating comparison of the results or to choose a set of more complex criteria embracing the heterogeneous symptoms with the goal of labelling the right children with the diagnosis. The 12-month period prevalence of asthma of 6.2% (4.2–9.0%) presented in this paper reflects the latter choice. On the other hand, our data are so extensive that different sets of diagnostic criteria can be applied for the purpose of comparison with other studies. As an example, we evaluated our prevalence of asthma using the diagnostic criteria by Lødrup Carlsen et al. (23), and then found a 12-month period prevalence of $50/404 = 12.4\%$ (9.5–16.0%), that is exactly twice our primary results. However, including the use of asthma medication in these diagnostic criteria for asthma might lead to an overestimation of the prevalence, as β_2 -agonists are often used as 'cough medicine' in Danish children by their general practitioners. The ISAAC Study assessed the 12-month period prevalence of asthma symptoms on the basis of the question: 'Has your child had wheezing or whistling in the chest in the past 12 months?' This question was also part of our questionnaire and a confirmatory answer was given by $26/404 = 6.4\%$ as opposed to Sweden: 10.2%, Germany: 12.8% and UK: 20.9% in the 6–7 yr age group in ISAAC Phase Three (18). No

other studies used the exact same criteria for asthma as we did, but studies on asthma in this age group in Scandinavia has shown figures similar to ours (24, 25).

The frequency of sensitization in children with asthma varies with age, varying diagnostic criteria and different methods of testing for sensitization. In our study, sensitization was present in 56% of children with asthma. This is in agreement with previous reports; Martinez et al. (26) found a positive SPT in 53% of persistent and late-onset wheezers at 6 yr of age and a large Swedish cross-sectional study of 7–8 yr old children disclosed a positive SPT in 52% of children with current asthma (25). Nevertheless the transferability of our results to the general population might be limited by the relatively small number of children with asthma in our cohort.

The 12-month period prevalence of rhinoconjunctivitis was 13.6% (10.6–17.3%). Most studies on the prevalence of allergic rhinoconjunctivitis in children are based on questionnaires alone and do not assess sensitization relevant for the symptoms. In the ISAAC Study, the use of the term 'allergic' is justified on the basis of questions with a rather high specificity for atopy. The 12-month period prevalence for allergic rhinoconjunctivitis in the 6–7 yr age group was 6.9% in Sweden and Germany and 10.1% in the UK (18), compared with our figure of allergic rhinoconjunctivitis of 5.7%, with the important difference that we assessed sensitization objectively. Objective assessment of sensitization was also performed in the MAS study (only S-IgE), revealing a lifetime prevalence of seasonal allergic rhinitis of around 13% at 6 yr of age (27). Although the MAS cohort is not entirely population based, this figure is high compared with ours, as the German study only report on rhinitis to grass and birch and uses a higher cut-off point for sensitization. In our opinion, the difference cannot be explained by the different epidemiological frequency measures as the difference between lifetime prevalence and period prevalence for this particular disease in this age group is small.

Questionnaire-based interview by a doctor, allergy testing for a variety of food allergens and controlled food challenges in an unselected cohort of children, provide a very solid ground for an estimate of the prevalence of food hypersensitivity. Food challenge was performed in all children with suspected food hypersensitivity, making our prevalence measure of 1.2% (0.4–3.0%) independent of assumptions. To our knowledge only one prior study assessed the

prevalence of food hypersensitivity in a population-based cohort of 6 yr-old children (28). In this study from Isle of Wight assessing food hypersensitivity in a manner similar to ours (except for S-IgE measurements) and including 798 6 yr old children, the prevalence of food hypersensitivity based on OCFs were 2.5% (1.5–3.8%) and based on DBPCFCs 1.6% (0.9–2.7%). Not all children could be food challenged in this study, so the prevalences were based on minor estimates. At 3 yr of age, the prevalence of food hypersensitivity in our cohort was 2.3% confirmed by oral challenges (6).

Frequency measures for urticaria in children are hard to come by, not least in population-based studies. Henz et al. (29) published a range of 2.1–6.7% based on several studies, comparable with our figure of 5.4% for urticaria in 6-yr-old children during the last year.

In conclusion, this study describes in detail the distribution of allergic diseases and sensitization in an unselected birth cohort of children at 6 yr of age. As the transferability of our results to the general population seems high, the fact that 25.7% of these children had a diagnosis of atopic dermatitis, asthma or rhinoconjunctivitis is concerning. Another important point in our findings was, that about half of the children diagnosed with these diseases were sensitized, advocating for future research also on the non-atopic aspect of these phenotypes. An overlap between the three diseases were, not surprisingly, significantly more frequent among sensitized children, arguing for the fact that sensitization is what connects these diseases to each other as also shown in a large Swedish study (30). Our results do not allow statements on time trends for these diseases, as this requires assessment of the prevalences at at least two different time points using the same methodology and the same diagnostic criteria in the same population.

Acknowledgments

We thank the children and their parents for their immense commitment to the project. A special acknowledgement to nurse Isabel Mejrup for her untiring work with the children and their families. Funding was obtained from The John and Birthe Meyer Foundation, Phadia (Uppsala, Sweden) donated all IgE measurements. There are no conflicts of interests.

References

1. KEIL T, KULIG M, SIMPSON A, et al. European birth cohort studies on asthma and atopic diseases: I. Comparison of study designs – a GALEN initiative. *Allergy* 2006; 61: 221–8.
2. JOHNKE H, NORBERG LA, VACH W, HOST A, ANDERSEN KE. Patterns of sensitization in infants and its relation

- to atopic dermatitis. *Pediatr Allergy Immunol* 2006; 17: 591–600.
3. JOHNKE H, VACH W, NORBERG LA, BINDSLEV-JENSEN C, HOST A, ANDERSEN KE. A comparison between criteria for diagnosing atopic eczema in infants. *Br J Dermatol* 2005; 153: 352–8.
4. JOHNKE H, NORBERG LA, VACH W, BINDSLEV-JENSEN C, HOST A, ANDERSEN KE. Reactivity to patch tests with nickel sulfate and fragrance mix in infants. *Contact Dermatitis* 2004; 51: 141–7.
5. NORBERG LA, JØHNKE H, BINDSLEV-JENSEN C, ANDERSEN KE, VACH W, HØST A. Environmental factors and atopic predisposition as predictors for the development of asthma, rhinoconjunctivitis and other atopic diseases in mucous membranes in childhood. PhD thesis. Denmark: University of Southern Denmark, 2003.
6. OSTERBALLE M, HANSEN TK, MORTZ CG, HOST A, BINDSLEV-JENSEN C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005; 16: 567–73.
7. OSTERBALLE M, ANDERSEN KE, BINDSLEV-JENSEN C. The diagnostic accuracy of the atopy patch test in diagnosing hypersensitivity to cow's milk and hen's egg in unselected children with and without atopic dermatitis. *J Am Acad Dermatol* 2004; 51: 556–62.
8. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989; 44 (Suppl. 10): 1–59.
9. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Position paper: allergen standardization and skin tests. *Allergy* 1993; 48 (Suppl. 14): 48–82.
10. DREBORG S, FOUCARD T. Allergy to apple, carrot and potato in children with birch pollen allergy. *Allergy* 1983; 38: 167–72.
11. American Thoracic Society. Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995; 152: 1107–36.
12. BINDSLEV-JENSEN C, BALLMER-WEBER BK, BENGTSOON U, et al. Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004; 59: 690–7.
13. HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; 92: 44–7.
14. NIGGEMANN B, JACOBSEN L, DREBORG S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006; 61: 855–9.
15. ORTOLANI C, ISPANO M, PASTORELLO E, BIGI A, ANSALONI R. The oral allergy syndrome. *Ann Allergy* 1988; 2: 47–52.
16. NIELSEN NH, SVENDSEN UG, MADSEN F, DIRKSEN A. Allergen skin test reactivity in an unselected Danish population. The Glostrup Allergy Study, Denmark. *Allergy* 1994; 49: 86–91.
17. NAGARAJA KANWAR AJ, DHAR S, SINGH S. Frequency and significance of minor clinical features in various age-related subgroups of atopic dermatitis in children. *Pediatr Dermatol* 1996; 13: 10–3.
18. ASHER MI, MONTEFORT S, BJORKSTEN B, et al. World-wide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 26: 368.
19. SCHULTZ LF, DIEPGEN T, SVENSSON A. The occurrence of atopic dermatitis in north Europe: an international questionnaire study. *J Am Acad Dermatol* 1996; 1: 760–4.
20. OLESEN AB, BANG K, JUUL S, THESTRUP-PEDERSEN K. Stable incidence of atopic dermatitis among children in Denmark during the 1990s. *Acta Derm Venereol* 2005; 85: 244–7.
21. ARSHAD SH, TARIQ SM, MATTHEWS S, HAKIM E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001; 108: E33.
22. SCHAFER T, KRAMER U, VIELUF D, ABECK D, BEHRENDT H, RING J. The excess of atopic eczema in East Germany is related to the intrinsic type. *Br J Dermatol* 2000; 143: 992–8.
23. LODRUP CARLSEN KC, HALAND G, DEVULAPALLI CS, et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy* 2006; 61: 454–60.
24. HOST A, HALKEN S, JACOBSEN HP, CHRISTENSEN AE, HERSKIND AM, PLESNER K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol* 2002; 13 (Suppl. 15): 23–8.
25. RONMARK E, LUNDBACK B, JONSSON E, PLATTS-MILLS T. Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in northern Sweden: prevalence rates and risk factor pattern. *Respir Med* 1998; 92: 316–24.
26. MARTINEZ FD, WRIGHT AL, TAUSSIG LM, HOLBERG CJ, HALONEN M, MORGAN WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 19: 332.
27. KULIG M, KLETTKE U, WAHN V, FORSTER J, BAUER CP, WAHN U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol* 2000; 106: 832–9.
28. VENTER C, PEREIRA B, GRUNDY J, CLAYTON CB, ARSHAD SH, DEAN T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol* 2006; 17: 356–63.
29. HENZ BM, ZUBERBIER T, GRABBE J, MONROE G. *Urticaria*. Berlin: Springer, 1998.
30. RONMARK E, PERZANOWSKI M, PLATTS-MILLS T, LUNDBACK B. Different sensitization profile for asthma, rhinitis, and eczema among 7–8-year-old children: report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatr Allergy Immunol* 2003; 14: 91–9.