

Relationship between aeroallergen and food allergen sensitization in childhood

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Summary

Background Previous studies measuring the prevalence of allergen sensitization have been relatively small and used small numbers of allergens. To effectively evaluate children with atopic disease, we need an accurate knowledge of which allergens are important.

Objective To measure the prevalence of sensitization within a large unselected birth cohort, to examine the associations between sensitization to different allergens and determine whether atopy can be defined by a small panel of allergens.

Methods The Avon Longitudinal Study of Parents and Children is a population-based birth cohort of 13 638 singletons surviving to 4 weeks of age. The cohort was skin tested at 7 years of age to house dust mite (*Dermatophagoides pteronyssinus*), grass pollens, cat, peanuts, mixed tree nuts and egg and one of three other panels: animal danders, foods or aeroallergens. Sensitization was defined as a weal diameter of ≥ 3 mm. The strength of associations between sensitization to different allergens was tested by calculating the odds ratio adjusted for sensitization to *D. pteronyssinus* and grass pollen and gender.

Results Valid data were obtained from 6412 singletons. Sensitization was most common to aeroallergens: grass pollens (8.5%), *D. pteronyssinus* (7.8%), cat (4.9%), *D. farinae* (3.6%), dog (2.7%), horse (1.4%), rabbit (1.4%). Of the foods tested, the most common sensitization was to peanut (1.4%) and mixed tree nuts (1.0%). More than 95% of subjects with sensitization to any of the 29 allergens tested were sensitized to one of grass, *D. pteronyssinus* or cat allergen. There were strong associations of multiple sensitizations both within and between different allergen classes (pollens, animals, foods, peanut and tree nuts).

Conclusions Seven-year-old children in the UK are primarily sensitized to aeroallergens, but also to peanuts and tree nuts. There are strong associations between sensitization within allergen groups as well as between allergen groups. Further studies are required to observe whether similar associations are seen with clinical allergy to these allergens.

Keywords aeroallergens, association, birth cohort, food allergens, prevalence, sensitization

Submitted 31 May 2004; revised 1 March 2005; accepted 22 April 2005

Introduction

It has been demonstrated that the prevalence of atopy is increasing. A recent international survey has suggested that up to a fifth of British teenagers had been diagnosed with asthma [1]; similar numbers had symptoms of rhinoconjunctivitis or eczema [2]. If we are to effectively evaluate children with atopic disease, we need an accurate knowledge of which aeroallergens and food allergens are important in this population, and what is the minimum number of allergens that we require to define whether a child is atopic. A number of previous studies have addressed this question but many have presented data on small, selected personal series derived from general hospital clinics or tertiary allergy centres [3]. Such data are likely to be

subject to considerable selection bias [4] and cannot provide information about prevalence. The prevalence of sensitization has also been examined within a number of cohort studies [5–11]. However, these studies have been relatively small and have been restricted to looking at only the most common allergens. Therefore, our knowledge of the prevalence of sensitization to less common allergens such as cockroach and latex comes only from case series [12, 13]. As atopic individuals are usually sensitized to more than one allergen, it is also useful to know whether sensitization to particular allergens is associated with sensitization to other ones. If such a question is to be successfully answered, a relatively large cohort is needed.

In this study, we have estimated the prevalence of sensitization to a wide range of aeroallergens and food allergens within the large birth cohort. Additionally, we assessed whether there was any association between sensitization to different allergens and whether atopy within this population could be defined by just using three aeroallergens (grass pollen, *Dermatophagoides pteronyssinus* and cat).

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Methods

Subjects

Subjects were participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective birth cohort of all babies with an expected delivery date between 1 April 1991 and 31 December 1992 [14]. The study was designed to provide a national resource for research (<http://www.alspac.bris.ac.uk>), allowing the interactions between genetic predisposition and environmental exposures in association with common childhood outcomes to be examined. The children taking part in the study were invited with their parents to dedicated research clinic during the period September 1998–September 2000. The clinic comprised a rotation of eight 20-min slots, of which one was devoted to skin prick testing. The ALSPAC cohort study receives ethical surveillance from the four local ethics committees (United Bristol Hospital Trust, Southmead, Frenchay and Weston Super Mare) as well as its own independent committee 'The ALSPAC Ethics and Law Advisory Committee'. All families gave informed, written consent for skin prick testing.

Skin prick testing

Parents were asked to stop short-acting antihistamine medication 48 h prior to the clinic and long-acting ones a week before attending. All subjects were tested on the volar surface of one forearm with six core allergens (*D. pteronyssinus*, mixed grass pollens, cat fur, peanut, mixed tree nuts and egg) plus negative (saline) and positive (histamine, 10 mg/mL) controls (ALK, Horsholm, Denmark). A panel of other allergens was tested on the other forearm. The use of one of three panels was rotated, with each being used for 1 week at a time. The panels were: other animal danders and soya (dog, horse, mouse, rabbit, guinea-pig, hamster, soya), additional foods (cod, sesame seed, cashew nuts, almond, walnut, hazelnut, brazil nut, pecan nut) and additional aeroallergens and food allergens (mixed tree pollens, *D. farinae*, *Alternaria alternata*, *Cladosporium herbarium*, *Aspergillus fumigatus*, cockroach, latex, milk). Thus, approximately one-third of the sample were tested with each panel of 'non-core' allergens. Prick tests were performed with 1 mm steel lancets (ALK), with a new lancet being used for each allergen, and maximum weal diameters were recorded 10 min later [15]. Personnel were trained to perform the prick testing by one experienced paediatrician.

Sensitization was recorded only if the maximum weal diameter of the histamine was greater than the saline weal diameter. Allergen sensitization was classified as positive if the maximum weal diameter was ≥ 3 mm. Atopy was defined as being sensitized to one of grass pollen, *D. pteronyssinus* or cat allergens.

Analysis

The prevalence of sensitization to each allergen is presented for the whole population and for the atopic and non-atopic subgroups. The association between sensitization to different allergens within and between allergen categories was examined using odds ratios (ORs). The higher the OR between a

pair of allergens, the greater the association between those two allergens. The OR was calculated from the ratio of the odds of sensitization to each allergen when sensitized to one particular core allergen to the odds of sensitization to the allergen when not sensitized to the core allergen. Adjusted ORs are also presented to allow for the confounding effect of gender and degree of atopy. Adjustment for the degree of atopy was made, as atopic subjects are more likely to be sensitized to more than one allergen. Similarly, very atopic subjects are more likely to be sensitized to multiple allergens. The degree of atopy was defined by the sum of the weal diameters of mixed grass pollens and *D. pteronyssinus* to give a categorical variable (0, 1–2, 3–4, >4 mm). Cat was not included for simplicity given that 93% of the subjects sensitized to cat, grass or *D. pteronyssinus* were sensitized to the latter two allergens. ORs were adjusted for gender, degree of atopy and an interaction term between the grass pollen and *D. pteronyssinus*. When either of these allergens formed part of the association being addressed, it was not used to adjust the OR. We looked at the relationship between a number of other potential confounders and the rate of sensitization (data not shown). None had an effect as large as gender, and therefore the ORs were also not adjusted for them.

The data analysis was restricted to singletons to avoid statistical problems of correlated sensitization within twins. All analyses were undertaken with Stata version 7. A *P*-value of 5% was taken to indicate statistical significance.

Results

Subjects

The research clinic was attended by 7623 subjects from the 13 638 surviving singletons in the cohort at 4 weeks of age; 6450 of these subjects had valid skin prick test (SPT) results. These 6450 subjects were similar to the cohort subjects for whom skin prick data were not available in terms of personal history of wheeze and rashes in joints and maternal history of eczema, asthma and hayfever. They were also similar to those who attended the research clinic but were not tested or did not have SPT result ($n = 1173$). Of the 6450 singletons with data, 6412 had complete valid data for histamine, saline, mixed grass pollens, *D. pteronyssinus* and cat allergen weals. Not all the subjects were able to tolerate skin prick testing to all of the non-core allergens (Table 1). Seventy children were found to have taken antihistamines, but most of these had a detectable skin reaction (≥ 3 mm) to histamine, and if so, they were included in the analysis. Their median age at clinic attendance was 90 months, with an inter-quartile range of 89–91 months; half were female.

Prevalence of sensitization

The prevalence of sensitization to each allergen tested is presented in Table 1. Sensitization (≥ 3 mm weal) was most common to mixed grass pollens (8.5%), *D. pteronyssinus* (7.8%), cat (4.9%), *D. farinae* (3.6%) and dog (2.7%). Peanut (1.4%) and mixed tree nuts (1%) are the most common food allergens to which children show sensitization (Table 1).

Table 1. Number of subjects with positive reactions to skin prick tests

Allergen	Number tested	Number with weal diameter ≥ 3 mm
Histamine (+ve)	6412	6412 (100.0)
Saline (–ve)	6412	0 (0.0)
Mixed grass pollens	6412	546 (8.5)
<i>Dermatophoides pteronyssinus</i>	6412	503 (7.8)
Cat	6412	314 (4.9)
Egg	5066	21 (0.4)
Peanut	6213	88 (1.4)
Mixed tree nuts	5848	61 (1.0)
Dog	2259	60 (2.7)
Horse	2255	32 (1.4)
Mouse	2129	8 (0.4)
Rabbit	2150	31 (1.4)
Guinea-pig	2148	13 (0.6)
Hamster	2147	2 (0.1)
Soya	1173	2 (0.2)
Cod	2061	1 (0.1)
Sesame seed	2003	3 (0.2)
Cashew nut	1998	8 (0.4)
Almond	1935	9 (0.5)
Walnut	1997	10 (0.5)
Hazelnut	2076	3 (0.1)
Brazil nut	1977	10 (0.5)
Pecan nut	1989	3 (0.2)
Mixed tree pollens	2053	15 (0.7)
<i>D. farinae</i>	2048	74 (3.6)
<i>Alternaria alternata</i>	2044	7 (0.3)
<i>Cladosporium herbarium</i>	2040	13 (0.6)
<i>Aspergillus fumigatus</i>	1942	3 (0.2)
Cockroach	1942	3 (0.2)
Latex	1877	3 (0.2)
Milk	2007	4 (0.2)

Data presented as the number (percentage) of children sensitized to each allergen based on singletons who had a valid histamine and saline control. The mixed tree nuts consisted of almond, brazilnut, hazelnut, cashew, pecan and walnut.

Subjects were divided into atopic and non-atopic in Table 2 according to whether or not they were sensitized (≥ 3 mm) to one of grass, *D. pteronyssinus* or cat allergen. Using this definition, 978 (15.3%) subjects were defined as atopic. This definition of atopy accurately assigned more than 95% of the subjects with sensitization to any of the allergens tested to the atopic group (Table 2).

Associations between sensitization to different allergens

The crude and adjusted ORs for the association between sensitization to each core aeroallergen and the other allergens are presented in Tables 3 and 4. Sensitization was found to be related to gender. For example, the odds ratio for sensitization to mixed grass pollens, *D. pteronyssinus* or cat was 0.64 (95% confidence interval 0.56–0.72) for females compared with male subjects. Adjusting the ORs for both gender and degree of atopy (based on the size of mixed grass pollens and *D. pteronyssinus* allergen weal unless they formed part of the association being addressed) reduced their magnitude but many relationships remained significant. There were particularly

Table 2. Percentage of positive reactions to the allergy skin prick tests by atopic status

Allergen	Number (%) of non-atopic children tested who gave a positive reaction	Number (%) of atopic children tested who gave a positive reaction
Mixed grass pollens	0/5434 (0)	546/978 (55.8)
<i>Dermatophagoides pteronyssinus</i>	0/5434 (0)	503/978 (51.4)
Cat	0/5434 (0)	314/978 (32.1)
Egg	3/4326 (0.07)	18/740 (2.4)
Peanut	20/5277 (0.4)	68/936 (7.3)
Mixed tree nuts	11/4978 (0.2)	50/870 (5.8)
Dog	4/1910 (0.2)	56/349 (16.1)
Horse	5/1906 (0.3)	27/349 (7.7)
Mouse	3/1796 (0.2)	5/333 (1.5)
Rabbit	4/1815 (0.2)	27/335 (8.1)
Guinea-pig	3/1814 (0.2)	10/334 (3.0)
Hamster	1/1813 (0.06)	1/334 (0.3)
Soya	0/965 (0)	2/208 (1.0)
Cod	1/1759 (0.06)	0/302 (0)
Sesame seed	1/1709 (0.06)	2/294 (0.7)
Cashew nut	3/1705 (0.2)	5/293 (1.7)
Almond	2/1648 (0.1)	7/287 (2.4)
Walnut	4/1703 (0.2)	6/294 (2.0)
Hazelnut	1/1774 (0.06)	2/302 (0.7)
Brazil nut	2/1689 (0.1)	8/288 (2.8)
Pecan nut	1/1698 (0.06)	2/291 (0.7)
Mixed trees pollens	4/1745 (0.2)	11/308 (3.6)
<i>D. farinae</i>	6/1741 (0.3)	68/307 (22.2)
<i>Alternaria alternata</i>	1/1739 (0.06)	6/305 (2.0)
<i>Cladosporium herbarium</i>	3/1737 (0.2)	10/303 (3.3)
<i>Aspergillus fumigatus</i>	1/1651 (0.06)	2/291 (0.7)
Cockroach	1/1651 (0.06)	2/291 (0.7)
Latex	1/1601 (0.06)	2/276 (0.7)
Milk	1/1705 (0.06)	3/302 (1.0)
Any allergen	41/5434 (0.75)	978/978 (100.0)

Data presented are numbers (percentages) of children sensitized to each allergen based on singletons who had a valid histamine and saline control. Atopy was also defined as being sensitized to either grass, *D. pteronyssinus* or cat allergens. A positive reaction is defined as an allergen weal ≥ 3 mm.

strong associations between allergens within the following groups: pollens, animals, house dust mite (HDM) and tree nuts.

The association between sensitization to peanut and tree nuts is described in Table 5. Similar associations in sensitization were seen within the animal allergens tested (Table 6). There was also a strong association between sensitization to *D. pteronyssinus* and cockroach (OR 24.2, 95% CI 1.7–350). Additionally, there was a strong association between sensitization to aeroallergens, such as grass pollen, *D. pteronyssinus* and cat, and peanuts and egg (Table 4).

Discussion

This study is the largest survey of skin prick testing among primary school children to be conducted in recent years. Additionally, we have used a much more extensive range of allergens compared with previous studies. The results show that the most prevalent aeroallergens to which 7-year-old

Table 3. Odds ratios (ORs) for positive skin prick tests

	Number tested	%	Core allergens				
			Mixed grass pollens	<i>Dermatophagoides pteronyssinus</i>	Cat	Peanut	Egg
Mixed grass pollens	6412	8.5	1.00	7.9*** (6.4–9.7)	9.5*** (7.4–12.1)	13.1*** (8.5–20.0)	17.8*** (7.4–43.3)
Mixed trees pollens	2053	0.7	24.8*** (8.4–73.5)	20.3*** (7.1–57.9)	14.4*** (5.0–41.4)	98.1*** (31.5–306)	107.4*** (16.2–714)
<i>Alternaria alternata</i>	2044	0.3	30.6*** (5.9–159)	17.4*** (3.9–78.5)	53.5*** (10.2–279)	15.0* (1.7–133)	–
<i>Cladosporium herbarium</i>	2040	0.6	19.9*** (6.4–62)	8.3*** (2.7–25.7)	25.4*** (8.4–77.2)	37.6*** (10.8–131)	–
<i>Aspergillus fumigatus</i>	1942	0.2	24.0** (2.2–267)	–	–	–	–
<i>D. pteronyssinus</i>	6412	7.8	7.9*** (6.4–9.7)	1.00	18.0*** (14.1–23.0)	11.7*** (7.6–17.9)	27.1*** (10.9–67.5)
<i>D. farinae</i>	2048	3.6	6.4*** (3.8–10.8)	125.7*** (64–247)	22.7*** (13.4–38.4)	21.8*** (9.7–49.0)	128.0*** (14.0–1166)
Cockroach	1942	0.2	6.0 (0.5–66)	25.7** (2.3–285)	9.8 (0.9–109)	35.7*** (3.1–406)	188.8*** (14.1–2524)
Cat	6412	4.9	9.5*** (7.4–12.1)	18.0*** (14.1–23.0)	1.00	20.9*** (13.5–32.4)	31.0 (12.9–74.4)
Dog	2259	2.7	19.6*** (11.4–33.7)	22.4*** (13.0–38.6)	107.9*** (56.5–206)	32.3*** (15.0–69.4)	19.5** (3.6–104)
Horse	2255	1.4	14.1*** (6.9–28.8)	19.5*** (9.5–40.2)	52.8*** (24.3–115)	24.0*** (9.5–60.5)	152.9*** (31.5–743)
Mouse	2129	0.4	3.3 (0.7–16.7)	7.2** (1.7–30.2)	32.0*** (7.5–136)	42.2*** (9.6–185)	67.7*** (6.6–698)
Rabbit	2150	1.4	20.2*** (9.5–42.8)	24.2*** (11.4–51.5)	23.0*** (11.0–47.9)	10.8*** (3.5–32.8)	12.2* (1.4–106)
Guinea-pig	2148	0.6	12.1*** (4.0–36.3)	14.4*** (4.8–43.4)	23.0*** (7.6–69.7)	21.2*** (5.5–81.1)	–
Hamster	2147	0.1	10.1 (0.6–161)	–	18.7* (1.2–301)	–	–
Peanut	6213	1.4	13.1*** (8.5–20.0)	11.7*** (7.6–17.9)	20.9*** (13.5–32.4)	1.00	66.8*** (27–165)
Mixed tree nuts	5848	1.0	15.0*** (9.0–25.0)	14.2*** (8.5–23.8)	20.0*** (11.9–33.6)	69.7*** (38.8–125)	46.6*** (17.2–126)
Sesame seed	2003	0.2	5.6 (0.5–61.6)	5.8 (0.5–63.8)	–	–	–
Cashew nut	1998	0.4	11.4*** (2.8–45.9)	11.7** (2.9–47.1)	7.0* (1.4–35.3)	11.4* (1.3–96.0)	–
Almond	1935	0.5	23.3*** (5.8–94.3)	5.8* (1.4–23.2)	5.8* (1.2–28.1)	9.8* (1.2–81.3)	24.4** (2.7–218)
Walnut	1997	0.5	11.4*** (3.3–39.9)	11.7*** (3.4–41.0)	5.2* (1.1–24.9)	37.2 (9.0–153)	33.9** (3.7–315)
Hazelnut	2076	0.1	22.7* (2.0–251)	5.8 (0.5–64.1)	10.8 (0.9–120)	–	106.9*** (8.8–1300)
Brazil nut	1977	0.5	7.6** (2.1–27.3)	17.7*** (4.9–63.2)	9.3** (2.3–36.4)	47.3*** (11.0–202)	–
Pecan nut	1989	0.2	22.7* (2.0–251)	23.5* (2.1–260)	–	39.7** (3.5–453)	–
Egg	5066	0.4	17.8*** (7.4–43.3)	27.1*** (10.9–67.5)	31.0 (12.9–74.4)	66.8*** (27–165)	1.00
Milk	1877	0.2	11.8* (1.6–84)	12.8* (1.8–91.6)	20.5** (2.9–147)	24.6** (2.5–245)	–
Latex	2007	0.2	25.0** (2.2–277)	6.5 (0.6–72.6)	10.1 (0.9–113)	164.6*** (14.4–1883)	–

Data presented are ORs (95% confidence interval) for association between sensitization to the core and other allergens. ORs represent the odds of sensitization to each allergen when sensitized to the core allergen compared with sensitization to the allergen when not sensitized to the core allergen. Sensitization is defined as a maximum weal diameter of ≥ 3 mm. *P*-values: *** < 0.001, ** < 0.01, * < 0.05.

A '–' means that no OR could be calculated as there were no cases that were sensitized to both allergens in that cell.

Table 4. Adjusted odds ratios (ORs) for positive skin prick tests

	Number tested	%	Core allergens				
			Mixed grass pollens	<i>Dermatophagoides pteronyssinus</i>	Cat	Peanut	Egg
Mixed grass pollens	6412	8.5	1.00	7.6*** (6.2–9.4)	3.9*** (2.9–5.2)	6.3*** (3.8–10.2)	6.0** (2.2–16.6)
Mixed tree pollens	2053	0.7	12.2*** (3.8–39.5)	7.3*** (2.3–23.2)	1.9 (0.5–7.8)	23.9*** (4.9–117)	245.1** (4.9–12359)
<i>Alternaria alternata</i>	2044	0.3	12.8** (2.3–71.6)	5.3* (1.0–12.6)	10.7* (1.4–84.4)	1.3 (0.1–13.4)	–
<i>Cladosporium herbarium</i>	2040	0.6	12.7*** (3.7–43.2)	3.5* (1.0–12.6)	9.8** (2.5–38.0)	10.6** (2.4–48.1)	–
<i>Aspergillus fumigatus</i>	1942	0.2	25.8** (2.2–307)	–	–	–	–
<i>D. pteronyssinus</i>	6412	7.8	7.6*** (6.2–9.4)	1.00	9.8*** (7.4–12.8)	4.9*** (3.0–7.9)	10.4*** (3.6–29.9)
<i>D. farinae</i>	2048	3.6	2.2* (1.1–4.3)	107.6*** (53.6–216)	3.0** (1.4–6.0)	5.6* (1.5–21.7)	34.1* (1.2–1008)
Cockroach	1942	0.2	2.1 (0.2–28.9)	24.2* (1.7–350)	1.3 (0.1–21.3)	7.8 (0.4–145)	34.3 (1.0–1217)
Cat	6412	4.9	3.9*** (2.9–5.2)	9.8*** (7.4–12.8)	1.00	5.4*** (3.1–9.3)	5.1** (1.8–14.1)
Dog	2259	2.7	7.6*** (4.1–14.0)	9.9*** (5.4–18.3)	36.2*** (16.6–78.6)	10.0*** (3.5–28.8)	1.4 (0.2–11.5)
Horse	2255	1.4	4.6*** (2.1–10.3)	8.2*** (3.6–18.3)	10.7*** (4.3–26.8)	5.4** (1.7–16.5)	29.5** (3.8–226)
Mouse	2129	0.4	1.7 (0.3–10.1)	5.3* (1.0–27.4)	31.8*** (5.1–19.7)	36.4*** (6.3–211)	57.7* (2.1–1603)
Rabbit	2150	1.4	6.0*** (2.6–14.0)	10.2*** (4.4–23.7)	3.0* (1.3–7.2)	1.3 (0.3–5.4)	0.7 (0.1–9.6)
Guinea-pig	2148	0.6	5.3* (1.4–19.3)	6.6** (1.9–23.4)	5.4* (1.4–20.0)	5.2* (1.1–24.6)	–
Hamster	2147	0.1	20.7* (1.3–335)	–	22.6 (0.7–70.2)	–	–
Peanut	6213	1.4	6.3*** (3.8–10.2)	4.9*** (3.0–7.9)	5.4*** (3.1–9.3)	1.00	11.9*** (4.3–32.9)
Mixed tree nuts	5848	1.0	6.4*** (3.6–11.5)	5.9*** (3.3–10.6)	4.5*** (2.4–8.3)	19.1*** (9.7–37.5)	7.1*** (2.4–21.2)
Sesame seed	2003	0.2	3.9 (0.2–74.7)	2.6 (0.2–32.8)	–	–	–
Cashew nut	1998	0.4	5.8* (1.1–31.7)	4.3 (0.9–21.3)	1.3 (0.2–8.8)	2.0 (0.2–20.9)	–
Almond	1935	0.5	23.4*** (5.0–109)	1.0 (0.2–4.8)	1.6 (0.3–10.1)	1.1 (0.1–10.5)	2.6 (0.2–31.9)
Walnut	1997	0.5	5.4* (1.2–24.9)	5.7* (1.3–24.4)	0.9 (0.1–5.8)	10.1** (1.9–55.2)	9.0 (0.5–166)
Hazelnut	2076	0.1	24.0* (1.7–335)	1.8 (0.1–24.4)	3.0 (0.1–71.6)	–	92.6** (4.2–2035)
Brazil nut	1977	0.5	2.0 (0.5–8.5)	11.3** (2.6–48.0)	1.8 (0.4–8.8)	13.7** (2.2–83.4)	–
Pecan nut	1989	0.2	9.3 (0.6–148)	9.9 (0.7–147)	–	6.5 (0.4–113)	–
Egg	5066	0.4	6.0** (2.2–16.6)	10.4*** (3.6–29.9)	5.1** (1.8–14.1)	11.9*** (4.3–32.9)	1.00
Milk	1877	0.2	8.7* (1.0–75.2)	5.4 (0.6–49.5)	3.9 (0.3–48.3)	4.0 (0.3–53.9)	–
Latex	2007	0.2	17.7* (1.3–238)	3.2 (0.3–39.7)	2.9 (0.1–65.4)	189.5** (6.6–5477)	–

ORs (95% confidence interval) represent the odds of sensitization to each allergen when sensitized to the core allergen compared with sensitization to the allergen when not sensitized to the core allergen. ORs are adjusted for gender and the size of mixed grass pollens and *D. pteronyssinus* allergen weal as a categorical variable (0, 1–2, 3–4, > 4 mm) as well as an interaction term between the two allergens. If the logistic regression contains either of these two allergens then it is not adjusted for the respective weal size. Sensitization is defined as a maximum weal diameter of ≥ 3 mm *P*-values: *** < 0.001, ** < 0.01, * < 0.05.

A '–' means that no OR could be calculated as there were no cases that were sensitized to both allergens in that cell.

Table 5. Adjusted odds ratios (ORs) for positive skin prick tests for peanuts, tree nuts and seeds

	N	%	Peanut	Mixed tree nuts	Sesame seed	Cashew nut	Almond	Walnut	Hazelnut	Brazil nut	Pecan nut
Peanut	6213	1.4	1.00								
Mixed tree nuts	5848	1.0	19.8*** (10.0–39.1)	1.00							
Sesame Seed	2003	0.2	–	–	1.00						
Cashew Nut	1998	0.4	1.79 (0.17–19.3)	57.5*** (8.9–370.0)	327.2*** (14.4–7427)	1.00					
Almond	1935	0.5	1.25 (0.13–11.8)	34.9*** (4.8–256.4)	46.3* (1.87–1144)	8.2 (0.64–105.7)	1.00				
Walnut	1997	0.5	8.8* (1.53–50.0)	136.3*** (21.6–860.9)	139.0** (4.3–4543)	107.6*** (14.3–810.7)	7.9 (0.56–110.2)	1.00			
Hazelnut	2076	0.1	–	26.1* (1.41–482.5)	–	50.6* (2.4–1078)	708.5*** (36.3–13811)	316.5*** (18.1–5545)	1.00		
Brazil nut	1977	0.5	12.7** (1.86–97.3)	–	154.8*** (6.9–3461.6)	88.5*** (10.6–734.9)	12.7 (0.94–172.1)	59.6*** (7.4–477.0)	–	1.00	
Pecan nut	1989	0.2	5.7 (0.32–102.1)	–	–	27.6* (1.31–583.2)	–	–	–	655.7*** (21.1–20339)	1.00

ORs (95% confidence interval) represent the odds of sensitization to the allergen in each row when sensitized to the allergen in each column compared with sensitization to the allergen when not sensitized to each column allergen. ORs are adjusted for gender and the size of mixed grass pollens and *Dermatophagoides pteronyssinus* allergen weal, as a categorical variable (0, 1–2, 3–4, >4 mm) as well as an interaction term between the two allergens. Sensitization is defined as a maximum weal diameter of ≥ 3 mm. *P*-values: *** < 0.001, ** < 0.01, * < 0.05.

A '–' means that no OR could be calculated as there were no cases that were sensitized to both allergens in that cell.

Table 6. Adjusted odds ratios (ORs) for positive skin prick tests for the animals

	N	%	Cat	Dog	Horse	Mouse	Rabbit	Guinea-pig	Hamster
Cat	6412	8.5	1.00						
Dog	2259	2.7	37.7*** (17.3–82.1)	1.00					
Horse	2255	1.4	11.1*** (4.4–27.9)	12.2 (4.7–31.9)	1.00				
Mouse	2129	0.4	31.8*** (5.3–190.8)	91.3*** (15.2–547.9)	188.4*** (26.8–1323)	1.00			
Rabbit	2150	1.4	3.0* (1.2–7.4)	7.4*** (2.8–19.5)	3.22* (1.09–9.53)	2.96 (0.21–41.8)	1.00		
Guinea-pig	2148	0.6	6.0** (1.6–22.2)	1.24 (0.23–6.66)	7.02** (1.69–29.2)	17.3* (1.31–228.2)	1.30 (0.18–9.3)	1.00	
Hamster	2147	0.1	25.4 (0.9–665.1)	–	–	–	0	167.9** (5.3–5295)	1.00

ORs (95% confidence interval) represent the odds of sensitization to the allergen in each row when sensitized to the allergen in each column compared with sensitization to the allergen when not sensitized to each column allergen. ORs are adjusted for gender and the size of mixed grass pollens and *Dermatophagoides pteronyssinus* allergen weal, as a categorical variable (0, 1–2, 3–4, >4 mm) as well as an interaction term between the two allergens. Sensitization is defined as a maximum weal diameter of ≥ 3 mm. *P*-values: *** < 0.001, ** < 0.01, * < 0.05.

A '–' means that no OR could be calculated as there were no cases that were sensitized to both allergens in that cell.

children were sensitized were grass pollens, *D. pteronyssinus* and cat, while the most prevalent food allergens were peanuts and tree nuts. The prevalence rates for the common aeroallergens seen in this study are similar to those seen in other cohort studies such as the Isle of Wight birth cohort [16]. The figures presented in this study also demonstrate how dependent the prevalence of sensitization is on the definition used. For example, 7.8% have a weal of at least 3 mm to *D. pteronyssinus* but only 4.4% have a weal to *D. pteronyssinus* that is at least the same size as their histamine control. Additionally a further 5.3% of the cohort had a weal to *D. pteronyssinus* that was smaller than both the 3 mm cut-off and their histamine control. This represents a large number of

individuals who may potentially become sensitized to the allergen through childhood.

Defining atopy

Atopy was originally defined as a predisposition to develop allergic diseases such as hayfever and asthma [17]. Atopy may be defined operationally as an increase in levels of total or specific IgE. However, there is a large overlap between atopic and non-atopic ranges [18], and the assays are expensive. Skin prick testing is cheaper than serum IgE measures and provides immediately available results; it is therefore perhaps the preferred means of defining sensitization. We have

pragmatically used sensitization to the three most common allergens to define atopy to ensure that as many possible atopic subjects are identified without the need to undertake testing with an extensive allergen panel. There is always the possibility of misclassifying a significant proportion of subjects when only a small group of allergens are used. However, despite testing subjects with 26 other allergens, a positive skin prick to this panel of grass pollen, *D. pteronyssinus* or cat identified all but 4% of subjects sensitized to these other allergens. Most of these misclassified subjects were sensitized to peanut and mixed tree nuts, with 20 (23%) and 11 (18%) allocated to the non-atopic group, respectively. Therefore, while this panel of three aeroallergens seems to be an easy and effective means of assigning atopy from an epidemiological viewpoint, adding peanut and mixed tree nuts in the panel would strengthen its ability to correctly identify those children who are only sensitized to food allergens.

Associations between sensitization to different allergens

As expected, our data demonstrate that there is a strong association between sensitization to allergens within biologically similar allergens. While this is probably because of cross-reactivity between similar allergens, it is possible that co-sensitization may occur to allergens found in the same environment, or the association may simply be related to the underlying atopic potential of the subject. In order to simplify the interpretation of the associations between sensitization to different allergens, we have attempted to control for the degree of atopy by adjusting results for the mixed grass pollens and *D. pteronyssinus* allergen weal diameters. The reaction to cat was not included to simplify the analysis as 93% of subjects were sensitized to either grass pollens or *D. pteronyssinus*. Many of these other children also had weals of less than 3 mm to either grass pollen or *D. pteronyssinus*. Atopy was defined in terms of the summated weal diameters as there is evidence that atopy is related to weal diameters [19].

We have shown that there is a very strong association between sensitization to cats and dogs as has been previously demonstrated [20]. The major allergens involved are epithelial allergens found in dander and saliva [21, 22]. This may represent cross-reactivity as where serum from a cat-allergic subject has been pre-incubated with dog dander, a substantial reduction in specific IgE binding has been demonstrated [23]. We also found significant degrees of association between the other animals tested. There are no studies addressing the association between clinical allergy to pets but it is known that allergy to cats or dogs is a strong risk factor for developing occupational allergy in animal workers [24]. Immunological cross-reactivity has been demonstrated within the grass pollen family [25, 26], tree pollens from the order Fagales (e.g. birch, alder and hazel) [27], HDM [28] and fish [29]. Our results also show a particularly high association between sensitization to *D. pteronyssinus* and cockroach. This is not unexpected as a major cockroach allergen Per a 7 has a high degree of homology with tropomyosins from invertebrates such as *D. pteronyssinus* [30].

A high degree of association between sensitization to peanut and some of the tree nuts is also seen in this group of children. Clinically, it is thought that half of patients with

peanut allergy also react to tree nuts [31, 32]. Peanut is a legume, not a tree nut and so it is possible that this association represents co-sensitization rather than cross-reactivity. Alternatively, many peanuts, other legumes and tree nuts all contain storage proteins called vicilins [33]. These may represent a common antigenic structure, thereby providing an immunological explanation for the association seen in sensitization to these foods. Other examples of co-sensitization in this cohort are the association between sensitization to grasses, *D. pteronyssinus* or cat and sensitization to peanut, tree nuts or egg. This has been previously noted, for example in the German Multicenter Allergy Study [34] and the Isle of Wight birth cohort [35].

Limitations of this study

There are a number of potential limitations in this study. Despite the large size of the ALSPAC cohort, the number of positive reactions to many allergens is low. This has resulted in wide confidence intervals for the associations between many of the allergens. Other studies have attempted to overcome this problem by assessing sensitization rates in consecutive referral to allergy clinics. Unfortunately, this approach can lead to selection bias. The ALSPAC cohort was recruited over a 21-month period, with children born between January and March being relatively under-represented. However, there was no evidence that the month of birth was related to sensitization in this cohort (data not shown). Lastly, we have presented data on the prevalence of sensitization and the rates of cross-sensitization to different allergens. Sensitization does not equate with clinical allergy, particularly with food allergens [36]. It is therefore important that the data presented here be interpreted in the light of the smaller published studies that have investigated the association between clinical allergy to different allergens [37].

Conclusions

In conclusion, it seems that 7-year-old children in the Avon area of the UK are primarily sensitized to grass pollens, *D. pteronyssinus* and cat, while the most prevalent food allergens are peanuts and tree nuts. There are many strong associations between sensitization to different allergens within and between related allergen groups, even after controlling for atopic disposition. Co-sensitization and cross-sensitization are important questions for children with allergic disease. Lastly, almost all of the sensitized subjects reacted to at least one of grass, *D. pteronyssinus* or cat allergen.

Acknowledgements

We are extremely grateful to all the mothers who took part, and to the midwives for their cooperation and help in recruitment. The whole ALSPAC Study Team comprises interviewers, computer technicians, laboratory technicians, clerical workers, research scientists, volunteers and managers who continued to make the study possible. This study could not have been undertaken without the financial support of the

Medical Research Council, the Wellcome Trust, UK government departments, medical charities and others. This particular analysis was funded by the British Lung Foundation and the Food Standards Agency (project T07001). The ALSPAC study is part of the WHO-initiated European Longitudinal Study of Pregnancy & Childhood.

References

- Kaur B, Anderson HR, Austin J et al. Prevalence of asthma symptoms, diagnosis, and treatment in 12–14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK). *BMJ* 1998; 316:118–24.
- Austin JB, Kaur B, Anderson HR et al. Hay fever, eczema, and wheeze: a nationwide UK study (ISAAC, international study of asthma and allergies in childhood). *Arch Dis Childhood* 1999; 81:225–30.
- Stelmach I, Jerzynska J, Stelmach W et al. Cockroach allergy and exposure to cockroach allergen in Polish children with asthma. *Allergy* 2002; 57:701–5.
- Sackett DL. Bias in analytic research. *J Chronic Dis* 1979; 32: 51–63.
- Tariq SM, Matthews SM, Stevens M, Hakim EA. Sensitization to *Alternaria* and *Cladosporium* by the age of 4 years. *Clin Exp Allergy* 1996; 26:794–8.
- Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. *BMJ* 1996; 313:514–7.
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999; 103:1173–9.
- Illi S, von Mutius E, Lau S et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001; 108:709–14.
- Bergmann RL, Edenharter G, Bergmann KE et al. Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 1998; 28:965–70.
- von Mutius E, Martinez FD, Fritsch C, Nicolai T, Reitmeir P, Thiemann HH. *BMJ* 1994; 308:692–5.
- Lombardi E, Stein RT, Wright AL, Morgan WJ, Martinez FD. The relation between physician-diagnosed sinusitis, asthma, and skin test reactivity to allergens in 8-year-old children. *Pediatr Pulmonol* 1996; 22:141–6.
- Hourihaue JO, Allard JM, Wade AM, McEwan AI, Strobel S. Impact of repeated surgical procedures on the incidence and prevalence of latex allergy: a prospective study of 1263 children. *J Pediatr* 2002; 140:479–82.
- Stelmach I, Jerzynska J, Stelmach W et al. Cockroach allergy and exposure to cockroach allergen in Polish children with asthma. *Allergy* 2002; 57:701–5.
- Golding J, Pembrey M, Jones R, ALSPAC Study Team. ALSPAC – the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatr Perinatal Epidemiol* 2001; 15:74–87.
- Malling H-J. Methods of skin testing. *Allergy* 1993; 48 (Suppl. 14):55–6.
- 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.
- Coca AF, Cooke RA. On the classification of the phenomena of hypersensitivity. *J Immunol* 1923; 8:163–71.
- Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997; 99:314–22.
- Skassa-Brociek W, Manderscheid JC, Michel FB, Bousquet J. Skin test reactivity to histamine from infancy to old age. *J Allergy Clin Immunol* 1987; 80:711–6.
- Schou C. Defining allergens of mammalian origin. *Clin Exp Allergy* 1993; 23:7–14.
- Schou C, Svendsen UG, Lowenstein H. Purification and characterization of the major dog allergen, Can f I. *Clin Exp Allergy* 1991; 21:321–8.
- Morgenstern JP, Griffith IJ, Brauer AW et al. Amino acid sequence of Fel dI, the major allergen of the domestic cat: protein sequence analysis and cDNA cloning. *Proc Natl Acad Sci USA* 1991; 88:9690–4.
- Spitzauer S, Pandjaitan B, Muhl S et al. Major cat and dog allergens share IgE epitopes. *J Allergy Clin Immunol* 1997; 99:t-6.
- Hollander A, Doekes G, Heederik D. Cat and dog allergy and total IgE as risk factors of laboratory animal allergy. *J Allergy Clin Immunol* 1996; 98:545–54.
- Laffer S, Spitzauer S, Susani M et al. Comparison of recombinant timothy grass pollen allergens with natural extract for diagnosis of grass pollen allergy in different populations. *J Allergy Clin Immunol* 1996; 98:652–8.
- Chakrabarty S, Lowenstein H, Ekramoddoullah AK, Kisil FT, Sehon AH. Detection of cross-reactive allergens in Kentucky bluegrass pollen and six other grasses by crossed radioimmuno-electrophoresis. *Int Arch Allergy Appl Immunol* 1981; 66:142–57.
- Niederberger V, Pauli G, Gronlund H et al. Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen: a quantitative IgE inhibition study with sera from different populations. *J Allergy Clin Immunol* 1998; 102:t-91.
- Heymann PW, Chapman MD, Platts-Mills TA. Antigen Der f I from the dust mite *Dermatophagoides farinae*: structural comparison with Der p I from *Dermatophagoides pteronyssinus* and epitope specificity of murine IgG and human IgE antibodies. *J Immunol* 1986; 137:2841–7.
- Hansen TK, Bindslev-Jensen C, Skov PS, Poulsen LK. Codfish allergy in adults: IgE cross-reactivity among fish species. *Ann Allergy Asthma Immunol* 1997; 78:187–94.
- Santos AB, Chapman MD, Aalberse RC et al. Cockroach allergens and asthma in Brazil: identification of tropomyosin as a major allergen with potential cross-reactivity with mite and shrimp allergens. *J Allergy Clin Immunol* 1999; 104:t-37.
- Loza C, Brostoff J. Peanut allergy. *Clin Exp Allergy* 1995; 25: 493–502.
- Hourihaue JO, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997; 27:634–9.
- Astwood JD, Silvanovich A, Bannon GA. Vicilins: a case study in allergen pedigrees. *J Allergy Clin Immunol* 2002; 110:26–7.
- Nickel R, Kulig M, Forster J et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997; 99:613–7.
- Tariq SM, Matthews SM, Hakim EA, Arshad SH. Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. *Pediatr Allergy Immunol* 2000; 11:162–7.
- Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000; 30:1540–6.
- Zeiger RS, Sampson HA, Bock SA et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr* 1999; 134:614–22.