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Sensitization to Common Allergens and Its Association With Allergic Disorders at Age 4 Years: A Whole Population Birth Cohort Study

Syed Hasan Arshad, DM, MRCP; Syed Mohammed Tariq, MRCP; Sharon Matthews, SRN; and Eluzai Hakim, MRCP

ABSTRACT. *Background.* Atopy is defined as the genetic propensity to develop immunoglobulin E antibodies in response to exposure to allergens and assessed by skin prick test responses to common allergens. Although it is generally agreed that atopy is an important risk factor for allergic diseases such as asthma, rhinitis, and eczema, the extent to which atopy accounts for these diseases is controversial.

Objective. We aim to describe the prevalence of sensitization to common allergens and investigate the degree of association of atopy (as defined by positive skin prick test to 1 or more common allergens) to asthma, rhinitis, and eczema in a birth cohort at the age of 4 years.

Methods. A birth cohort of 1456 children was recruited over a 14-month period (1989–1990). These children have been seen previously at 1 and 2 years of age. At 4 years, 1218 children were reviewed and an interview was administered or postal questionnaire was completed for the presence of allergic diseases (asthma, rhinitis, and eczema). Additionally, in 981 children, skin prick tests with a battery of 12 common allergens were performed. Allergens were house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, cat, dog, *Alternaria alternata*, *Cladosporium herbarum*, cow's milk, hen's egg, soya, cod, wheat, and peanut. A mean wheal diameter of at least 3 mm greater than the negative control was taken as positive. This analysis is confined to the 981 (67% of the original population) who also had skin prick tests to the standard battery.

χ^2 tests were used to test the univariate association between each allergic disease and positive skin test. Multiple logistic regression analysis was performed to obtain the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the independent effect of sensitization to each allergen on allergic disease, adjusting for the effect of sensitization to other allergens. To ascertain how much of allergic disease is attributable to atopy, we estimated the population-attributable risk. This was calculated with the formula: $P(R - 1) / R$ where R is the OR for the allergic disease under consideration and P is the proportion of atopy in children with that disease.

Results. Children who were skin prick-tested at 4 years were similar in most characteristics to the rest of the population, except that they had a higher prevalence of allergic disease. Allergic disorders (asthma, rhinitis, and eczema) were present in 276 (28.1%) of 981. One hundred ninety-two (19.6%) children were atopic (posi-

tive reaction to 1 or more allergens). Sensitization to inhalant allergens was relatively common (19.2%) as compared with food allergens (3.5%). House dust mite (11.9%), grass pollen (7.8%), and cat (5.8%) were the most common positive reactions. A test to the 4 most common allergens (house dust mite, grass pollen, cat, and *A alternata*) could detect 94% of the atopic children. Sensitization to the 4 most common allergens was strongly associated with the presence of allergic disorders. There was a graded effect with the potent allergens, such as house dust mite, having the greatest impact. For example, 50% of children sensitized to house dust mite had asthma as opposed to 44% sensitized to cat, 42% sensitized to grass pollen, and 32% sensitized to *A alternata*. Overall, 68.4% of children sensitized to house dust mite had asthma, eczema, and/or rhinitis. The respective figures for grass pollen, cat, and *A alternata* were 64.9%, 66.7%, and 57.4%. The proportion of children sensitized to cat was not higher in households with cat ownership (households with cats: 5.1% [19/374]; households without cats: 6.2% [36/580]; not significant [NS]). Similarly, no difference was seen in sensitization to dog in households with and without dogs (households with dogs: 1.8% [5/282]; households without dogs: 2.8% [19/673]; NS). Boys were atopic more often than girls at this age (male: 112 of 497 [22.5%] vs female: 80 of 484 [16.5%]; OR: 1.47, 95% CI: 1.07–2.02). Male preponderance was observed with most allergens, but this was statistically significant only for house dust mite (male: 75/497 [15.1%] vs female: 42/484 [8.7%]; OR: 1.87; CI: 1.25–2.79) and grass pollen (male: 51/497 [10.3%] vs female: 26/484 [5.4%]; OR: 2.01; CI: 1.23–3.29).

An independent effect of allergen sensitization on asthma was observed only with house dust mite with an OR of 8.07 (CI: 4.60–14.14). The highest independent risk for rhinitis was sensitization to grass pollen (OR: 5.02; CI: 2.21–11.41), and for eczema, sensitization to peanut (OR: 4.65; CI: 1.02–21.34).

The majority of children (98/192) were sensitized to >1 allergen. A graded effect was observed with the risk of allergic disease in the child increasing with the number of positive skin prick test reactions. This effect was consistent throughout the spectrum of allergic diseases (asthma, eczema, and rhinitis). Nearly 80% of the children with positive skin test reactions to 4 or more allergens had asthma, eczema, and/or rhinitis compared with 20%, if they were nonatopic.

The prevalence of atopy in asthmatic children was 44%. With an OR of 4.56, the population-attributable risk was calculated to be 35%. Fifty-five percent of children with rhinitis were atopic, and the OR of rhinitis was 5.85. Therefore, 46% of the cases of rhinitis could be attributable to atopy. The population-attributable risk of atopy for eczema was 32% (the prevalence of atopy in children with eczema: 43%; and the OR for the development of eczema: 3.86).

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Conclusion. Atopy is closely associated with asthma, rhinitis, and eczema at 4 years of age, with a direct and linear relationship. However, the proportion of cases of allergic disease attributable to atopy is <50%. We propose a model for the development of allergic disorders, where 30% to 40% of cases of allergic disease (asthma, eczema, and rhinitis) in early childhood are attributable to atopy and 60% to 70% of cases could be accounted for by organ-based and other factors. *Pediatrics* 2001;108(2). URL: <http://www.pediatrics.org/cgi/content/full/108/2/e33>; atopy, allergic diseases, asthma, eczema, rhinitis, skin-prick test.

ABBREVIATIONS. IgE, immunoglobulin E; OR, odds ratio; CI, confidence interval.

Asthma, rhinitis, and eczema often are termed allergic or atopic diseases. These terms are used loosely and interchangeably. Allergy is defined as an exaggerated (immune-mediated) response to various proteins (allergens). Atopy is defined as the genetic propensity to develop immunoglobulin E (IgE) antibodies in response to exposure to allergen and is assessed by positive skin-prick test responses, which may contribute to the development of the clinical disorder (phenotype). The term "atopy" should be used only when there is evidence of IgE-mediated allergy. Some allergic disorders clearly are predominantly atopic, such as hay fever or peanut allergy. However, diseases such as asthma and perennial rhinitis may or may not be atopic. Indeed, even in atopic allergic diseases, an IgE-initiated mechanism is part of a complex cascade of cellular and humoral immune responses after allergen exposure.¹ In adults, asthma and rhinitis are classified as nonallergic when total IgE is normal and/or specific IgE to common allergens is not detected in the serum or on skin-prick test. Even in children, when atopy is presumed to be the cause in the vast majority of children, similar symptoms occur in nonatopic individuals.² The relationship of atopy to asthma and other allergic diseases is not understood clearly.^{2,3} Atopic eczema is, by definition, related to atopy; however, the cause-and-effect relationship is not established. Eczema and sensitization to food and inhalant allergens both are common in early childhood.⁴

In an individual, the presence of atopy may be confirmed by high levels of specific IgE or total IgE in the serum or by positive responses to skin-prick test. A number of studies examined the association between asthma and atopy in both adults and children.^{2,5-8} Some of these studies were in large unelected populations,^{2,5,7,8} whereas others were smaller case-control studies.⁶ One birth cohort study from New Zealand examined the association of childhood asthma with sensitization to common aeroallergens, based on skin-prick testing performed at 13 years of age.⁹⁻¹¹ The authors reported that sensitivity to house dust mite and to cat were significant risk factors for asthma, whereas sensitivity to grass pollen was not significant.⁹ Our birth cohort study describes the relationship of atopy to symptoms of allergic disease in early childhood.

In 1989 to 1990, a whole-population birth cohort was recruited on the Isle of Wight to study the development of and risk factors for allergic disorders through childhood. These children were followed up at 1, 2, and 4 years to determine the presence of allergic disorders and atopy, as assessed by positive skin-prick test to 1 or more common allergens. Previous reports of the 4-year follow-up examined the risk factors for allergic diseases⁴ and the influence of cord IgE.¹² This analysis specifically describes the pattern of sensitization to common allergens at the age of 4 years and the relationship of atopy to allergic diseases.

METHODS

For a period of 14 months (January 1989 to February 1990), the parents of all children born on the Isle of Wight ($n = 1536$) were approached, and an interview-administered questionnaire was completed. The study was approved by the local research ethics committee, and informed consent was obtained from all parents. After excluding adoptions, perinatal deaths, nonresidents, and refusals, 1456 children were available for inclusion in this prospective study. At birth, information was obtained on family history of allergic diseases, presence of pets, smoking in the house, and birth weight. Data on social class were available for 723 children from the maternity records, as this information was not sought at the time of recruitment.

These children were reviewed at 1,¹³ 2,¹⁴ and 4^{4,12} years of age. At 1 and 2 years, a questionnaire seeking information on symptoms suggestive of allergic disease in the child was completed. Those with symptoms of allergic disease were seen in the clinic and administered a skin-prick test. At 4 years of age, all children and their parents were invited to attend the allergy clinic. A total of 981 children (67% of the original cohort) attended the clinic, and an interview-administered questionnaire was completed, physical examination was conducted, and skin-prick tests were performed on these children. Questionnaire (postal or telephone) information was available for an additional 237 children ($n = 1218$; 84% of the original cohort). Some of the families had moved from the Isle of Wight, and others did not want the child to be skin-prick tested. Questionnaire information related to the presence or otherwise of allergic disease and details of environmental factors such as parental smoking, exposure to pets, housing conditions, and birth order were updated.

Diagnostic Criteria for Atopic Disease

Information was obtained by the study physicians (E.A.H., S.M.T., S.H.A.) regarding the presence of allergic symptoms. For asthma, information included the presence and frequency of cough and wheezing, physician-diagnosed asthma, and treatment given. For eczema, the presence of typical rash and its distribution and duration were established. For rhinoconjunctivitis, the presence of nasal (discharge, blockage, and recurrent sneezing) and eye (itching, watering) symptoms was recorded. A physical examination was performed for the relevant signs. A clinical diagnosis was made as to the presence of asthma, eczema, and rhinitis. The minimum criteria for the diagnosis of asthma included 3 or more separate episodes of wheeze and/or cough, each lasting at least 3 days. Eczema constituted recurrent, scaly, pruritic, erythematous rash in a typical distribution lasting for 6 weeks or more. A diagnosis of rhinitis required frequent or seasonal symptoms of nasal discharge and/or blockage and recurrent sneezing.

Skin-Prick Tests

A panel of 6 inhalant and 6 food allergens was used. These included house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, cat, dog, *Alternaria alternata*, *Cladosporium herbarum*, cow's milk, hen's egg, soya, cod, wheat, and peanut. Standardized extracts were used when available. All extracts were from Biodiagnosics (Reinbek, Germany). Histamine (0.1%) in phosphate-buffered saline and physiologic saline were used as positive and negative controls, respectively. Two study nurses performed all of the tests. Children were advised not to take antihistamines for 72

hours before the clinic appointment. Commercially available lancets (Medipoint, Inc, Mineola, NY) were used to prick the epidermis through the allergen extract drops. The tests were read at 15 minutes, and mean wheal diameters were calculated (sum of the longest diameter and the diameter perpendicular to it divided by 2). In the presence of a positive control (≥ 3 mm), a mean wheal diameter of at least 3 mm greater than the negative control was taken as positive. Surrounding erythema was ignored. The data also were analyzed using a 2-mm cutoff, as has been used in some studies.⁹

Statistical Analysis

All data were coded and entered into the database module of the statistics software SPSS PC+ V4 (SPSS Inc, Chicago, IL). All subsequent analysis was performed using this package. χ^2 tests were used to test the univariate association between each allergic disease and positive skin-prick test (Fisher's exact test was used when appropriate). Multiple logistic regression analysis was performed to obtain the adjusted odds ratios (OR) and 95% confidence intervals (CI) for the independent effect of sensitization to each allergen on allergic disease, adjusting for the effect of sensitization to other allergens. In the regression model, asthma, rhinitis, and eczema were entered as the dependent variable and the results of skin-prick tests to allergens included in the standard battery were entered as covariates. To assess how much of allergic disease is attributable to atopy (defined as positive skin-prick test) in this population, we estimated the population-attributable risk.³ This was calculated with the formula $P(R - 1)/R$, where R is the OR for the allergic disease under consideration and P is the proportion of atopy in children with that disease.

RESULTS

Information on the prevalence of allergic diseases was available on 1218 (84%) children. This analysis is confined to the 981 (67%) of the original population, who also had skin-prick tests to the standard battery. Table 1 shows the characteristics of children with and without skin-prick tests. There were no significant differences in gender, family history of allergic disease, birth characteristics, exposure to environmental tobacco smoke, and presence of pets. Allergic

disorders (asthma, rhinitis, or eczema) were present in 317 of the 1218 (26%) when information was available and 276 (28.1%) of 981 who were skin-prick tested at 4 years. A total of 238 children were not seen at the 4-year follow-up. Information was available on 231 of these children from the previous follow-ups at 1 and 2 years (Table 1). Disproportionately more of these children belonged to a lower socioeconomic group. When allergic disease at 1 or 2 years was compared, there was little difference between those who were not seen at 4 years and those who were not skin-prick tested. However, children who were skin-prick tested at 4 year showed a higher prevalence of allergic disease at 1 and 2 years as well.

A total of 192 children (19.6%) were atopic (positive reaction to 1 or more allergens); using a cutoff of 2 mm increased the number of children regarded as atopic to 202 (20.6%). Sensitization to inhalant allergens was relatively common (19.2%) as compared with food allergens (3.5%). There were only 3 children who were sensitized solely to a food allergen. House dust mite (11.9%), grass pollen (7.8%), and cat (5.8%) were the most common positive reactions (Fig 1). The proportion of children who were sensitized to cat was not higher in households with cat ownership (households with cat: 5.1% [19 of 374], households without cat: 6.2% [36 of 580]; not significant). Similarly, no difference was seen in sensitization to dog in households with and without dogs (households with dog: 1.8% [5 of 282]; households without dog: 2.8% [19 of 673]; not significant). The 4 most common allergens (house dust mite, grass pollen, cat, and *A alternata*) could detect 94% of the atopic children.

Sensitization to the 4 most common allergens was strongly associated with the presence of allergic dis-

TABLE 1. Characteristics of Children Who Completed Questionnaire and Were Skin Tested, Who Completed Questionnaire but Were Not Skin Tested, and Who Were Not Seen at 4-Year Follow-Up

Characteristic	SPT Done [n/Total n (%)]	SPT Not Done [n/Total n (%)]	Not Seen at 4 Years [n/Total n (%)]
Family history of allergic disease			
Maternal	332/977 (34.0)	79/236 (33.5)	88/238 (37.0)
Paternal	254/977 (26.0)	57/235 (24.3)	62/231 (26.8)
Sibling	212/564 (37.6)	38/114 (33.3)	53/138 (38.4)
Maternal IgE (mean [SE])	112.91 (7.52) (n = 680)	117.39 (16.08) (n = 162)	109.71 (15.97) (n = 152)
Allergic diseases at 4 y			
Asthma	161/981 (16.4)	20/234 (8.5)	NA
Rhinitis	60/980 (6.1)	5/234 (2.1)	NA
Eczema	124/981 (12.6)	21/233 (9.0)	NA
Any allergic disease*	276/981 (28.1)	41/236 (17.4)	NA
Allergic diseases at 1 or 2 y			
Asthma	144/946 (15.2)	21/200 (10.5)	32/231 (13.9)
Rhinitis	169/946 (17.9)	19/200 (9.5)	29/231 (12.6)
Eczema	161/946 (17.0)	21/200 (10.5)	14/231 (6.1)
Any allergic disease*	336/946 (35.5)	48/200 (24.0)	52/231 (22.5)
Male gender	497/981 (50.7)	127/237 (53.6)	122/238 (51.3)
High cord IgE (>0.5 ku/L)	112/858 (13.1)	27/206 (13.1)	ND
Low birth weight (<2.5 kg)	38/954 (4.0)	5/231 (2.2)	9/231 (3.9)
Exposure to cigarette smoke	373/981 (38.0)	92/237 (38.8)	NA
Low socioeconomic group†	308/586 (52.6)	66/137 (48.2)	93/135 (68.9)
Cat in the house	374/954 (39.2)	76/204 (37.3)	NA
Dog in the house	283/956 (29.6)	69/200 (34.5)	NA

NA indicates information not available at 4 year; ND, not done.

* Asthma and/or rhinitis and/or eczema.

† Social classes 4 and 5 according to the Registrar General's classification, information collected at recruitment.

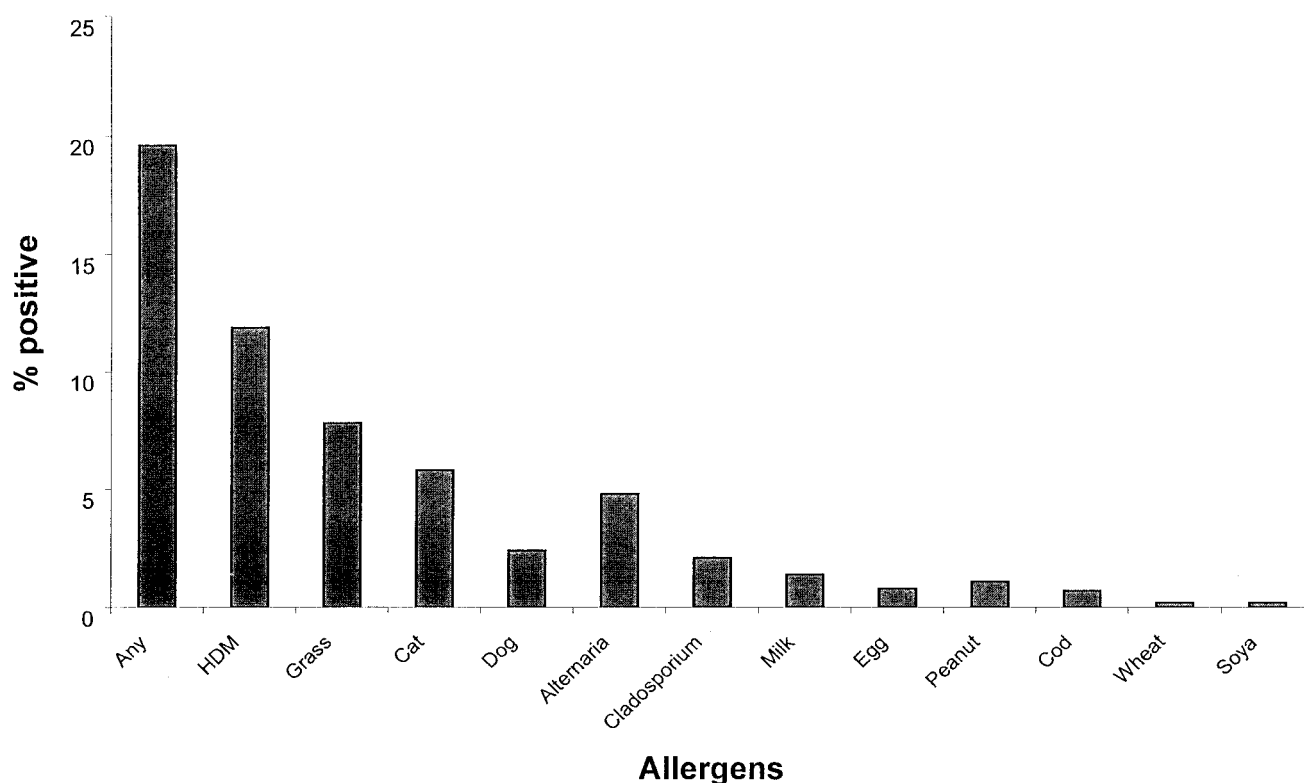


Fig 1. Sensitization to common food and inhalant allergens in an unselected population of children aged 4 years (% indicates percentage of children whose tests were positive to the respective allergen in the population studied).

orders (Table 2); using a cutoff of 2 mm for skin-prick test positivity did not have a significant effect on this association. For example, 59 (36.5%) children with asthma were sensitized to house dust mite with a 3-mm cutoff. The corresponding figure for a 2-mm cutoff was 64 (39.8%). Sensitization to other inhalant allergens (dog and *C herbarum*) and some of the food allergens also showed an association (data not shown). There was a graded effect with the potent allergens, such as house dust mite, having the greatest impact. For example, 50% of children who were

sensitized to house dust mite had asthma, as opposed to 44% who were sensitized to cat, 42% who were sensitized to grass pollen, and 32% who were sensitized to *A alternata* (Table 3). Overall, 68.4% children who were sensitized to house dust mite had asthma, eczema, and/or rhinitis.

Boys were atopic more often than girls at this age (boys: 112 of 497 [22.5%] vs girls: 80 of 484 [16.5%]; OR: 1.47; CI: 1.07–2.02; $P = .02$). Male preponderance was observed with most allergens, but this was statistically significant for house dust mite (boys: 75 of 497 [15.1%] vs girls: 42 of 484 [8.7%]; OR: 1.87; CI: 1.25–2.79; $P = .002$) and grass pollen (boys: 51 of 497 [10.3%] vs girls: 26 of 484 [5.4%]; OR: 2.01; CI: 1.23–3.29; $P = .004$).

An independent effect of allergen sensitization on asthma was observed only with house dust mite (OR: 8.07; Table 4). For rhinitis, grass pollen and egg were independent risk factors. The development of eczema was influenced by sensitization to 3 major inhalant (house dust mite, grass pollen, and cat) and 2 food (egg and peanut) allergens, confirming the atopic nature of eczema at this age.

The majority of children (98 of 192) were sensitized to >1 allergen. A graded effect was observed with the risk of allergic disease in the child increasing with the number of positive skin-prick test reactions (Fig 2). This effect was consistent throughout the spectrum of allergic diseases (asthma, eczema, and rhinitis). Nearly 80% of children with positive skin-prick test reactions to 4 or more allergens had asthma, eczema, and/or rhinitis compared with 20% if they were nonatopic.

TABLE 2. Allergic Sensitization in 4-Year-Old Children With Common Allergic Disorders (Univariate Analysis)

Sensitization	Yes [n (%)]	No [n (%)]	OR (95% CI)
Asthma	<i>n</i> = 161	<i>n</i> = 820	
Any allergen	71 (44.1)	121 (14.8)	4.56 (3.16–6.57)
House dust mite	59 (36.6)	58 (7.1)	7.60 (5.00–11.53)
Grass pollen	32 (19.9)	45 (5.5)	4.27 (2.62–6.97)
Cat	25 (15.5)	32 (3.9)	4.53 (2.60–7.88)
<i>Alternaria</i>	15 (9.4)	32 (3.9)	2.55 (1.35–4.82)
Rhinitis	<i>n</i> = 60	<i>n</i> = 920	
Any allergen	33 (55.0)	159 (17.3)	5.85 (3.42–10.00)
House dust mite	24 (40.0)	93 (10.1)	5.93 (3.39–10.37)
Grass pollen	19 (31.7)	58 (6.3)	6.89 (3.76–12.62)
Cat	9 (15.0)	48 (5.2)	3.21 (1.49–6.90)
<i>Alternaria</i>	7 (11.7)	40 (4.4)	2.90 (1.24–6.79)
Eczema	<i>n</i> = 124	<i>n</i> = 857	
Any allergen	53 (42.7)	139 (16.2)	3.86 (2.59–5.75)
House dust mite	35 (28.2)	82 (9.6)	3.72 (2.36–5.84)
Grass pollen	30 (24.2)	47 (5.5)	5.50 (3.32–9.12)
Cat	24 (19.4)	33 (3.9)	5.99 (3.41–10.55)
<i>Alternaria</i>	15 (12.2)	32 (3.7)	3.58 (1.88–6.83)

TABLE 3. Skin-Prick Test Positivity to Common Allergens and Point Prevalence of Asthma, Eczema, Rhinitis, and Any Allergic Disease

Allergen	Asthma [n (%)]	Rhinitis [n (%)]	Eczema [n (%)]	Any Allergic Disease [n (%)]
House dust mite				
Positive (n = 117)	59 (50.4)	24 (20.5)	35 (29.9)	80 (68.4)
Negative (n = 864)	102 (11.8)	36 (4.2)	89 (10.3)	196 (22.7)
Grass pollen				
Positive (n = 77)	32 (41.6)	19 (24.7)	30 (39)	50 (64.9)
Negative (n = 904)	129 (14.3)	41 (4.5)	94 (10.4)	226 (25.0)
Cat				
Positive (n = 57)	25 (43.9)	9 (15.8)*	24 (42.1)	38 (66.7)
Negative (n = 924)	136 (14.7)	51 (5.5)	100 (10.8)	238 (25.8)
<i>Alternaria</i>				
Positive (n = 47)	15 (31.9)*	7 (14.9)*	15 (31.9)	27 (57.4)
Negative (n = 933)	145 (15.5)	53 (5.7)	108 (11.6)	248 (26.6)
Peanut				
Positive (n = 11)	4 (36.4) ^{NS}	3 (27.3)*	6 (54.5)	6 (54.5) [†]
Negative (n = 967)	156 (16.1)	57 (5.9)	117 (12.1)	269 (27.8)
Egg				
Positive (n = 8)	3 (37.5) ^{NS}	5 (62.5)	4 (50.0)*	6 (75)*
Negative (n = 972)	157 (16.1)	55 (5.7)	119 (12.2)	269 (27.7)

NS indicates not significant. $P < .001$ except where indicated by * or †.

* $P < .01$.

† $P < .05$.

TABLE 4. Adjusted OR and CI for the Independent Risk of Allergic Disorder With Sensitization to Common Allergens (Logistic Regression Analysis, $n = 842$)

Allergen	Asthma (OR [CI])	Rhinitis (OR [CI])	Eczema (OR [CI])
House dust mite			
Positive (n = 97)	8.07 (4.60–14.14)‡	2.19 (0.92–5.17)	1.95 (1.04–3.66)*
Negative (n = 745)			
Grass pollen			
Positive (n = 71)	1.53 (0.76–3.08)	5.02 (2.21–11.41)‡	2.92 (1.49–5.72) [†]
Negative (n = 771)			
Cat			
Positive (n = 53)	0.89 (0.40–1.97)	0.68 (0.23–2.05)	2.70 (1.23–5.92) [†]
Negative (n = 789)			
Peanut			
Positive (n = 11)	0.65 (0.13–3.36)	2.98 (0.54–16.54)	4.65 (1.02–21.34)*
Negative (n = 831)			
Egg			
Positive (n = 6)	1.85 (0.28–12.37)	18.43 (2.06–164.71) [†]	6.08 (0.88–42.01)
Negative (n = 836)			

Sensitization to other allergen, included in the model but found to be nonsignificant were, dog, *Alternaria*, *Cladosporium*, milk, wheat, cod, and soya.

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

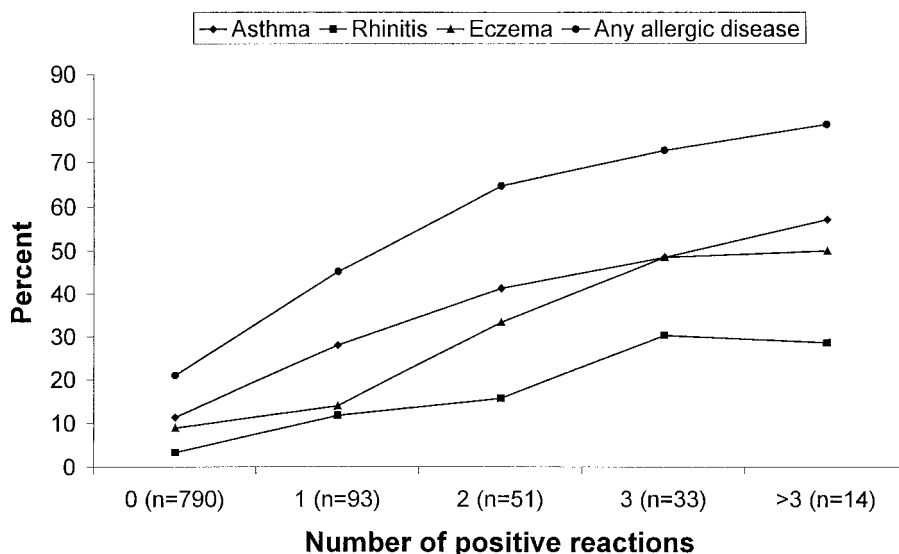
The prevalence of atopy in children with asthma was 44% (Table 2). With an OR of 4.56, the population-attributable risk was calculated to be 34%. There was essentially no change in the population-attributable risk (34.6%) when a 2-mm cutoff was used (atopy in children with asthma: 45%; OR: 4.34). Fifty-five percent of children with rhinitis were atopic (OR: 5.85). Therefore, 46% cases of rhinitis could be attributable to atopy. The population-attributable risk of atopy for eczema was 32% (prevalence: 43%; OR: 3.86).

DISCUSSION

Overall 475 children (33%) either were not seen or did not have a skin-prick test at 4 years (Table 1). The prevalence of allergic disease was higher in children who were skin-prick tested compared with those who were not skin-prick tested. There was minimal

difference in the prevalence of allergic disease at 1 or 2 years in those who did not have a skin-prick test and those who were not seen at 4 years. Family history of allergic disease and environmental risk factors (except for social class) were similar in all groups. It is likely that children who were not seen at 4 years had a similar prevalence of allergic disorders to those who were seen but not skin-prick tested. This may have skewed our results toward a higher prevalence of atopy in children who were skin-prick tested and biased the results toward a stronger association of atopy with allergic disease. However, the prevalence of atopy (19.6%) in those who were skin-prick tested was lower than reported in children in other studies,^{9,15,16} which argues against the possibility that a highly sensitized subpopulation came forward for skin-prick testing. Children who were not seen at 4 years more commonly belonged to a

Fig 2. Risk of allergic diseases in a child increases with the number of positive skin-prick tests.



lower socioeconomic group, but this is unlikely to have significantly effected the prevalence of atopy.⁴

As this cohort was recruited during a period of 14 months, with inclusion of January and February births over 2 consecutive years, there was a higher number of winter births (winter: 381; spring: 295; summer: 279; autumn: 263). This potentially could introduce a bias with regard to the season of birth effect. In this cohort, however, season of birth had influenced neither the development of allergic disorders nor allergen sensitization at 4 years of age.⁴

Foods are common allergens in early childhood. As the child grows, foods are replaced by inhalant allergens.¹⁷ Our study confirms that sensitization to food allergens becomes relatively uncommon (3%) by the age of 4. A recent report¹⁶ describing the natural course of sensitization to food and aeroallergens showed a decrease in the sensitization to food allergen from 10% at 1 year to 3% at 6 years. At the same time, sensitization to inhalant allergens increased from 1.5% at 1 year to 26% at 6 years of age. In our study, 60% of the atopic children could be identified with skin-prick test to house dust mite alone and 94% when 4 common inhalant allergens were included in the skin-prick test battery. This is a useful guide when screening children for atopy.

The prevalence of atopy of 19.6% was somewhat lower than reported in other studies.^{9,15,16} Some authors, using a smaller wheal size of ≥ 2 mm as the cutoff for skin-prick test positivity, reported a higher prevalence of atopy.⁹ Using a cutoff of 2 mm in this population did not increase the prevalence of atopy significantly, either in the whole population or among children with asthma. The lowest limit of skin-prick test reactivity that reliably predicts radioallergosorbent assay test positivity is, in fact, a larger wheal size of 4 to 5 mm.¹⁸ Therefore, a 3-mm cutoff for skin-prick test positivity, which is used commonly in clinical and epidemiologic studies,^{19–22} was thought to be more appropriate. Most other studies assessed children who were 6 years or older.^{8,9,19–22} An explanation for somewhat lower prevalence rate could be the age of our childhood popu-

lation. At the age of 4, children have grown out of food sensitization (as confirmed by this study) but may not yet have acquired sensitization to aeroallergens.

Some less common inhalant allergens, such as tree pollen, horse, or *Aspergillus*, were not included in the standard battery. The need to include common food allergens in the battery at this age meant that the number of inhalant allergens had to be restricted. Although, in theory, it is possible that a child may be sensitized solely to an uncommon allergen not included in the battery, this would be a rare occurrence. We believe that by using this panel, we were able to detect most of the atopic children among those given skin-prick tests in this cohort. Unfortunately, serum total and specific IgE levels were not measured to strengthen the validity of skin-prick test responses. However, total IgE may be within the age-adjusted normal range in some atopic individuals.²³

Several studies^{9,24} noted a positive correlation between the prevalence and severity of asthma and the number and size of positive skin-prick tests. Our findings are similar, showing a linear relationship with a higher prevalence of allergic disease in children who react to >1 allergen (Fig 2). Unfortunately, a valid correlation of the number of skin-prick test responses to clinical indicators of severity of allergic diseases could not be made because only a minority had severe disease.

Our study confirms previous reports of a higher prevalence of atopic sensitization in boys than in girls.^{10,20,25} A statistically significant difference was observed only with house dust mite and grass pollen sensitization, although the trend was similar for all allergens tested.

It is a common belief that the allergic disorders are almost always atopic, especially in children. Evidence supporting this hypothesis is the clustering of the disorders in families and the presence of allergic sensitization in a majority of children with these disorders. A number of studies suggested an association of atopy with asthma.^{2,5–9,25} Indeed, for asthma,

there is considerable epidemiologic evidence for the causative role of IgE.^{6,8,26} However, there are few studies in which this relationship was studied in a homogenous, unselected population recruited at birth.^{7,9} Overall, these studies suggest a positive relationship between atopy, as assessed by skin-prick test responses or IgE, and asthma. Sears et al⁹ showed a strong independent risk of house dust mite and cat but not grass pollen sensitization on the development of asthma and bronchial hyperresponsiveness. Our study confirms this observation and extends it to other allergic diseases (rhinitis and eczema). House dust mite sensitization was found to be the most important risk for asthma, with an OR of 8.07. This is consistent with the humid climate of Isle of Wight. We previously showed house dust mite concentrations in homes in the Isle of Wight to be extremely high.²⁷ Peat et al,¹⁵ in their study of different regions of Australia, found house dust mite to be the most important risk factor in coastal regions, whereas *A alternata* acquired a higher significance in the inland with a dry climate. In Isle of Wight, cat or grass pollen sensitization was not an independent risk factor of asthma, although grass pollen sensitization was closely associated with rhinitis.

The relationship of allergen exposure, sensitization, and the development of allergy-related disease is complex. In a recent study, Lau et al⁷ reported a strong association of dust mite and cat allergen sensitization with respiratory symptoms and bronchial hyperresponsiveness during the first 7 years of life. However, they failed to demonstrate a consistent relationship between dust mite and cat allergen exposure and respiratory allergic manifestation. Platts-Mills et al⁸ confirmed, as does our study and previous reports,^{9,22} that mite and cat sensitization are strong independent risk factors for asthma. However, whereas increased mite allergen exposure leads to increased sensitization, increased cat allergen exposure stimulates IgG antibody production and decreases the risk of sensitization to cat allergen.⁸ In our study, having a cat or a dog at home did not influence the prevalence of sensitization to their allergens. Our data also support the suggestion that sensitization to various indoor allergens has a differential effect on the development of allergic diseases, with house dust mite having the highest risk and molds the lowest. Sensitization to the common molds *A alternata* and *C herbarum* was observed in a number of children who had no evidence of clinical disease.²⁸

Although it generally is agreed that atopy is an important risk factor for allergic disease, the extent to which atopy accounts for these diseases is controversial. Simple IgE-mediated disorders, such as hay fever and peanut allergy, clearly are attributable to sensitization to pollen and peanut, respectively. Asthma, eczema, and perennial rhinitis are, however, more complex disorders. Evidence supporting the role of total IgE in asthma includes the correlation of elevated serum levels of IgE with self-reported asthma symptoms²⁹ and airway hyperresponsiveness.^{26,30} However, other studies cast doubt on the role of total IgE as an important indicator of respiratory allergic diseases.³¹ In the African popu-

lation, serum levels of IgE have been reported to be higher in people who do not have asthma than in people who do.³² Similar symptoms occur in the absence of sensitization (nonallergic or intrinsic disease). Even in allergic eczema, non-IgE-mediated inflammatory mechanisms may play a significant role. For asthma, rhinitis, and eczema, it may be argued that the primary abnormality is genetically determined and affects the airway/nasal epithelium³³ and/or dermis/epidermis.³⁴

So how much of allergic disease is attributable to atopy? Pearce et al³ attempted to solve this, in relation to asthma, by a meta-analysis of the published articles describing the association of asthma and atopy. Their analysis included studies in which atopy was defined as either positive skin-prick test responses or high serum IgE. They concluded that the proportion of asthma cases that attributable to atopy averaged between 30% and 40%, in both adults and children. Our results confirm this observation in 4-year-old children not only for asthma but also for rhinitis and eczema. We propose a model for the development of allergic disorders, in which 30% to 40% of cases of chronic allergic disease in early childhood are attributable to atopy and 60% to 70% of cases could be accounted for by organ-based and other factors.

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**Sensitization to Common Allergens and Its Association With Allergic Disorders
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