

House dust mite sensitization in toddlers predicts current wheeze at age 12 years

Caroline J. Lodge, MBBS, GradDipEpi,^{a,c} Adrian J. Lowe, BBS, MPH, PhD,^{a,c} Lyle C. Gurrin, BSc(Hons), PhD,^a David J. Hill, MBBS, FRACP,^c Clifford S. Hosking, MD, FRACP, FRACPA,^e Rida U. Khalafzai, MBBS, MPH,^a John L. Hopper, BA, BSc, MSc, PhD,^a Melanie C. Matheson, BSc, MAppSc, PhD,^a Michael J. Abramson, MBBS, BMedSc(Hons), PhD, FRACP, FAFPHM,^f Katrina J. Allen, MBBS, BMedSc, FRACP, PhD,^{b,c,d} and Shyamali C. Dharmage, MBBS, MSc, MD, PhD^{a,c} Melbourne and Newcastle, Australia

Background: Identification of children at risk of developing asthma provides a window of opportunity for risk-reducing interventions. Allergen sensitization might identify high-risk children.

Objective: We sought to determine whether skin prick tests (SPTs) to individual allergens up to age 2 years predict wheeze at age 12 years.

Methods: In a birth cohort of 620 children oversampled for familial allergy, sensitization was assessed by using SPTs (monosensitized, polysensitized, or either) to 6 allergens at ages 6, 12, and 24 months. Wheeze and eczema were recorded 18 times during the first 2 years. Current wheeze was recorded at age 12 years. Adjusted associations were evaluated by multiple logistic regression.

Results: A positive SPT to house dust mite (HDM) at age 1 or 2 years predicted wheeze at age 12 years (adjusted odds ratio: 1 year, 3.31 [95% CI 1.59-6.91]; 2 years, 6.37 [95% CI, 3.48-11.66]). Among wheezy 1-year-olds, those who were HDM sensitized had a 75% (95% CI, 51% to 91%) probability of wheeze at age 12 years compared with a 36% (95% CI, 23% to 50%) probability among those not sensitized. Among eczematous 1-year-olds, those who were HDM sensitized had a 67% (95% CI, 45% to 84%) probability of wheeze at age 12 years compared with a 35% (95% CI, 25% to 45%) probability among those not sensitized. Among 1-year-old children with

both eczema and wheeze, the probability of wheeze at age 12 years was 64% (95% CI, 35% to 87%) if HDM sensitized and 50% (95% CI, 26% to 74%) if not.

Conclusion: HDM sensitization at age 1 or 2 years in wheezing and eczematous children at increased familial allergy risk predicts asthma and may inform management of these high-risk groups. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Birth cohort, asthma, wheeze, eczema, sensitization, house dust mite

Asthma is an important global health issue that is estimated to affect at least 300 million persons worldwide.¹ The International Study of Asthma and Allergies in Childhood (ISAAC) reported the prevalence of current wheeze in 6- to 7-year-olds at 2.8% to 37.6% across 37 countries and in 13- to 14-year-olds at 3.4% to 31.2% across 56 countries.² Identification of those who are likely to have asthma provides a window of opportunity for interventions aimed at prevention of disease and subsequent inflammatory lung remodeling. Stein and Martinez³ found that “significant loss of pulmonary function” in persistent wheezers “seems to occur after birth but before 6 years of age.” Therefore it is important to identify these at-risk groups in early childhood because children with wheeze can exhibit lung changes by the time of school entry.⁴

Of all factors previously considered in the literature, early-life atopy measured by using skin prick tests (SPTs) or serum allergen-specific IgE measurement has one of the strongest and most consistent relationships with subsequent asthma.⁵⁻¹⁴ However, most atopic children are sensitized to more than 1 allergen, with the number of different sensitizations increasing over time.¹⁵ Therefore it is difficult to determine whether one allergen is a greater contributor than others to the subsequent asthma risk. Sensitization to a single allergen can only be considered a true predictor of asthma if it is significantly associated with the risk of asthma in both monosensitized and polysensitized subjects. Although the associations between early-childhood allergen sensitization and asthma⁵⁻¹⁴ have been examined in many studies, most of these have measured sensitization at one time point,⁸ after the age of 4 years,^{5,6,8,9,11} or both. However, few have addressed issues concerning temporal relationships, and none have assessed these relationships in children in the first 2 years of life with monosensitization versus polysensitization. Hence there has been limited ability to determine which allergic sensitizations are independent predictors of subsequent asthma.

From ^aCentre for MEGA Epidemiology and ^bthe Department of Paediatrics, University of Melbourne, Melbourne; ^cMurdoch Children's Research Institute and ^dthe Department of Allergy, Royal Children's Hospital, Melbourne; ^eEmeritus, John Hunter Children's Hospital, Newcastle; and ^fPublic Health and Preventative Medicine, Monash University, Melbourne.

Initial support for the study was from Nestlé Australia, and the 12-year follow-up was supported by the Asthma Foundation of Victoria. C.J.L. is supported by the Sidney Myer Health Fund and the National Health and Medical Research Council of Australia (NHMRC). A.J.L., L.C.G., J.L.H., M.C.M., and S.C.D. are supported by the NHMRC. K.J.A. is supported by the Charles and Sylvia Viertel Charitable Foundation.

Disclosure of potential conflict of interest: M. J. Abramson was part of the Landmark Symposium for GlaxoSmithKline and receives research support from Reckitts Benckiser. D. Hill has received past support from Nutricia, SHS International, and Nestlé for research, and has presented lectures at sponsored meetings. The rest of the authors have declared that they have no conflict of interest.

Received for publication December 14, 2010; revised June 10, 2011; accepted for publication June 13, 2011.

Reprint requests: Caroline J. Lodge, MBBS, GradDipEpi, School of Population Health, Faculty of Medicine, Dentistry & Health Sciences, Centre for Molecular, Environmental, Genetic & Analytic Epidemiology, Level 3, 207 Bouverie St, University of Melbourne, Victoria 3010, Australia. E-mail: clodge@unimelb.edu.au.

0091-6749/\$36.00

© 2011 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2011.06.038

Abbreviations used

aOR: Adjusted odds ratio
HDM: House dust mite
ISAAC: International Study of Asthma and Allergies in Children
MACS: Melbourne Atopy Cohort Study
SPT: Skin prick test

Other factors strongly associated with the development of asthma and intimately related to sensitization include a history of early-life wheeze and early-onset eczema.¹⁶

By using a longitudinal birth cohort study, our primary aim was to examine whether early-life sensitization to individual allergens was associated with wheeze at age 12 years. A secondary aim was to examine whether this association differed in children with early wheeze or early eczema.

METHODS**Study population**

The Melbourne Atopy Cohort study (MACS) is a longitudinal, birth cohort study comprising 620 babies enrolled before birth by recruiting pregnant women living in Melbourne, Australia. Eligible babies had at least 1 first-degree family member with a history of eczema and/or asthma and/or allergic rhinitis and/or severe food allergy. The 620 children were born between March 24, 1990, and November 1, 1994.

Data collection

An allergy-trained research nurse conducted telephone surveys with the babies' mothers every 4 weeks from birth to 15 months, at 18 months, annually from 2 to 7 years, and at 12 years.

Detailed demographic and environmental data were obtained during pregnancy. The follow-up interviews included specific questions related to the development of allergic/atopic diseases and symptoms, other infant illnesses or conditions, contact with health care professionals, and medications used. The 12-year surveys included validated asthma questions from ISAAC.¹⁷

SPTs

SPTs were offered to the entire cohort at 6 months, 1 year, and 2 years. Allergens tested were cow's milk, egg white, peanut, house dust mite (HDM), rye grass, and cat dander (Bayer, Spokane, Wash). A trained research nurse placed a single drop of each allergen on the infant's back, and the skin was pricked with a lancet. Histamine (1 mg/mL) was used as the positive control. The SPTs were read at 10 to 15 minutes, and wheal diameters were measured. In accordance with other studies in young children,¹⁸⁻²⁰ a positive SPT response was defined as a mean wheal diameter of 2 mm or greater.

Definitions

Early wheeze at 6 months, 1 year, and 2 years was defined as having at least 1 episode of doctor-diagnosed asthma, wheezy bronchitis, bronchitis, or bronchiolitis by 6 months, 1 year, and 2 years, respectively.

At the 12-year follow-up, *current wheeze* was defined by a positive response to the following ISAAC question: "Has your child ever had wheezing or whistling in the chest in the past 12 months?"¹⁷ Current wheeze was further divided into severe wheeze or mild wheeze. *Severe wheeze* was defined as 4 or more episodes of wheeze or any use of corticosteroids (inhaled or oral) in the past 12 months. *Mild wheeze* was defined as current wheeze that was not severe. *Eczema* was defined as any rash that had been treated with steroid creams (excluding rashes on the scalp and nappy area). *One-year and 2-year eczema* were defined as eczema at any time by 1 or 2 years of age, respectively.

Parental and sibling food allergy, asthma, hay fever, and eczema were all defined by parental responses at recruitment.

Parental atopy was defined as an average wheal diameter of 3 mm or greater for any allergen when tested to a panel of 6 common allergens tested within the first 2 years of the child's birth. Allergens tested for parents were the same as those above for children. *Monosensitization* was defined as sensitization to only 1 allergen. *Polysensitization* was defined as sensitization to 2 or more allergens. *Other sensitization* was defined as monosensitization or polysensitization to an allergen or allergens other than the allergen of interest. *Socioeconomic status* was defined by whether 1 or both parents were receiving social security benefits.

Statistical analysis

Two-sample comparison tests (*t* tests for continuous values and χ^2 tests for proportions) of baseline demographic and medical characteristics were used to assess potential differential loss to follow-up (see Table E1 and the Methods section in this article's Online Repository at www.jacionline.org). Multiple logistic regression models were used to investigate the associations between individual sensitization to 1 or multiple allergens and wheeze at age 12 years while adjusting for possible confounding by measured factors.

In the initial analysis sensitizations for different allergens were highly correlated, giving rise to issues of interpretation associated with multicollinearity. We therefore created 4 categories of sensitization for each allergen at age 1 and 2 years, respectively: not sensitized to any allergen (reference category), sensitized to the allergen of interest only (monosensitized), sensitized to the allergen of interest and 1 or more other allergens (polysensitized), and not sensitized to the allergen of interest but sensitized to 1 or more other allergens (other sensitized). Multiple logistic regression models were then fitted to examine the associations between this 4-level categorical variable of each allergen and the presence of wheeze at age 12 years while adjusting for confounders. Confounders were chosen from the following list: parental age, asthma, food allergy, hay fever, eczema, smoking, and socioeconomic status; weight of the infant at 4 weeks (as a surrogate for birth weight); participant's sex, eczema, and wheeze; sibling number and atopy; and cat and carpet in the home. Confounders remained in the final model if there was a change of 10% or more in the odds ratio of the relevant sensitization category. Interactions with sex, eczema, and early wheeze; maternal and paternal asthma; and maternal and paternal sensitization to any allergen, aeroallergens, and dust mite only were tested. The relevant associations were stratified by eczema and early wheeze.

The sensitization data at 6 months were not used in this analysis because the numbers of children who were sensitized at 6 months of age, when divided into categories of monosensitization and polysensitization, were very small.

Ethics

Ethics approval was obtained from the Mercy Maternity Hospital's Human Research Ethics Committee. Informed consent was provided by all participating mothers.

Stata software (release 10.0; StataCorp, College Station, Tex) was used for all analyses.

RESULTS

Baseline demographics of MACS have already been published.²¹⁻²⁴ Briefly, parents of the MACS cohort were predominantly well educated (59% of mothers and 61% of fathers attended university), Australian born (87% of mothers and 83% of fathers), and of high socioeconomic status (4% of mothers and 3% of fathers were receiving social security benefits at baseline). More than half (51%) of the participants were male, and all children had at least 1 immediate family member with "allergic disease" (74% with ≥ 2 affected family members). Further details concerning which family members had allergic disease are

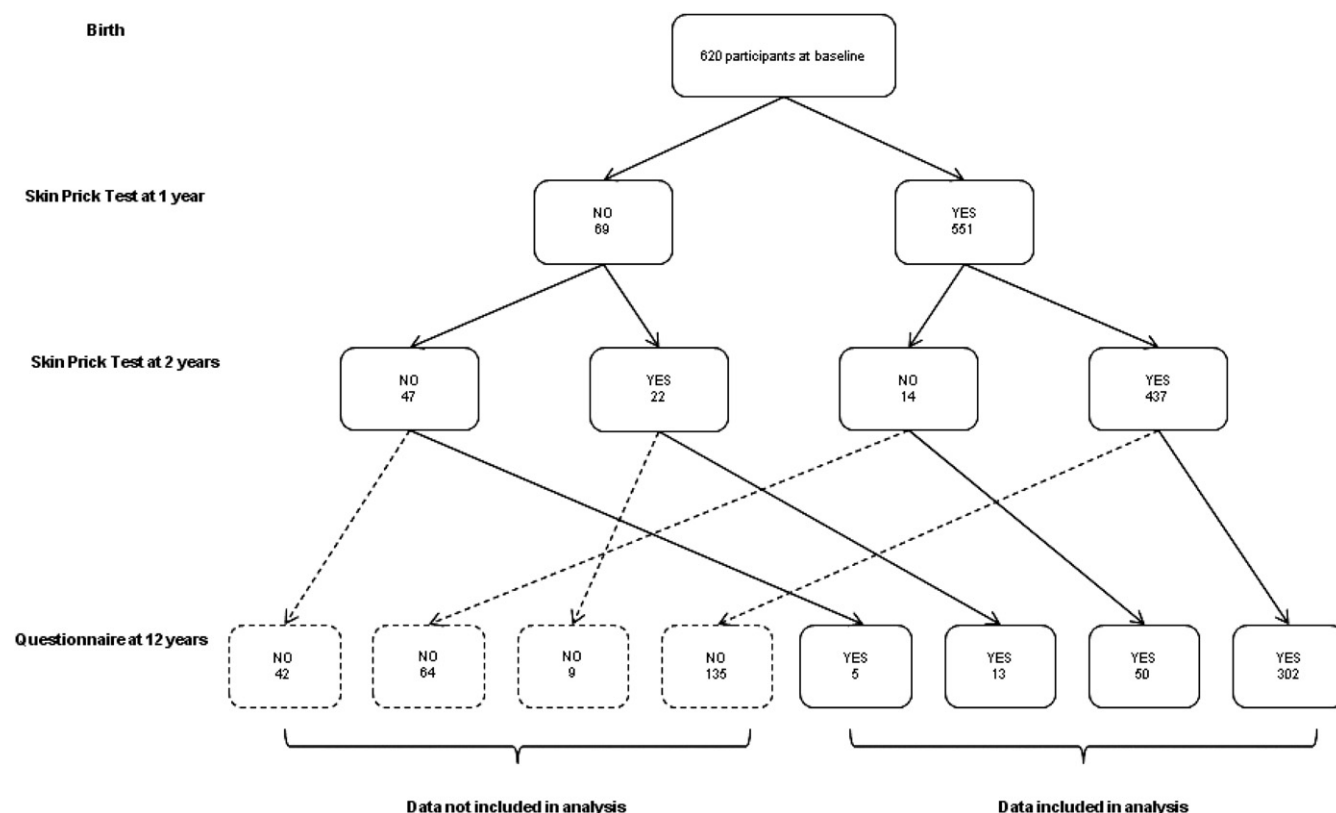


FIG 1. Flow of participants.

provided in Table E2 in this article's Online Repository (available at www.jacionline.org).

Of the 620 participants in the study at baseline, there were 551 and 459 who had SPTs at 1 and 2 years, respectively, and 365 who provided data for the 12-year follow-up study (Fig 1). Those who attended at each time point were not different from those who did not attend on a wide range of baseline characteristics (including family history of allergic disease, parental smoking, parental atopy, prior SPT results, and early-life wheeze; see Tables E1 and E3 in this article's Online Repository at www.jacionline.org).

Prevalence of sensitization

The prevalence of positive SPT responses by age is shown in Fig 2. By 6 months of age, 26% (147/560) of the participants had a positive response to at least 1 allergen. This increased to 33% (183/551) by 1 year and 36% (165/459) by 2 years. At 6 months and 1 year, the most common sensitization was to egg white, accounting for 15% (81/560) and 19% (106/551), respectively. However, by 2 years, dust mite was the most common at 23% (105/459). There was no difference in the prevalence of sensitization to each allergen in the total cohort when compared with the subgroup who had allergic outcomes measured at age 12 years (see Table E4 in this article's Online Repository at www.jacionline.org).

Of those sensitized by 6 months, 56% (83/147) were monosensitized, and 44% (64/147) were polysensitized. At 1 year, there were 48% (87/183) monosensitized and 52% (96/183) polysensitized, and at 2 years, of the 165 sensitized children, 82 (49.7%) were monosensitized, and 83 (50.3%) were polysensitized. There

was a significant increase in polysensitization between 6 months and 1 year ($P = .014$).

Asthma/wheeze

By 6 months, 11% (95% CI, 8% to 14%) of the participants had early wheeze. This increased to 21% (95% CI, 18% to 25%) by 1 year and 33% (95% CI, 29% to 37%) by 2 years. At the 12-year follow-up (interquartile range, 10-12.9 years) the prevalence of current wheeze was 28% (95% CI, 24% to 33%). This accounted for 102 of the 365 children with information at this time.

Early-life sensitization and current wheeze at age 12 years

Table I describes the relationships between different profiles of early allergen sensitization and wheeze at age 12 years. Only the 1-year data are shown; however, the 1- and 2-year data were concordant in all associations (2-year data are shown in Table E5 in this article's Online Repository at www.jacionline.org).

At 1 and at 2 years, only HDM monosensitization was positively associated with increased risk of wheeze at age 12 years when compared with those who were not sensitized to any allergen (nonatopic). Children monosensitized to HDM at 1 year had approximately 8 times the odds of wheeze at age 12 years, and those monosensitized at 2 years had approximately 9 times the odds of wheeze at age 12 years when compared with those who were not sensitized to any allergen.

When a particular allergen sensitization was considered in concert with other allergen sensitization (polysensitized), almost every allergen (except cat dander at age 1 year) was significantly

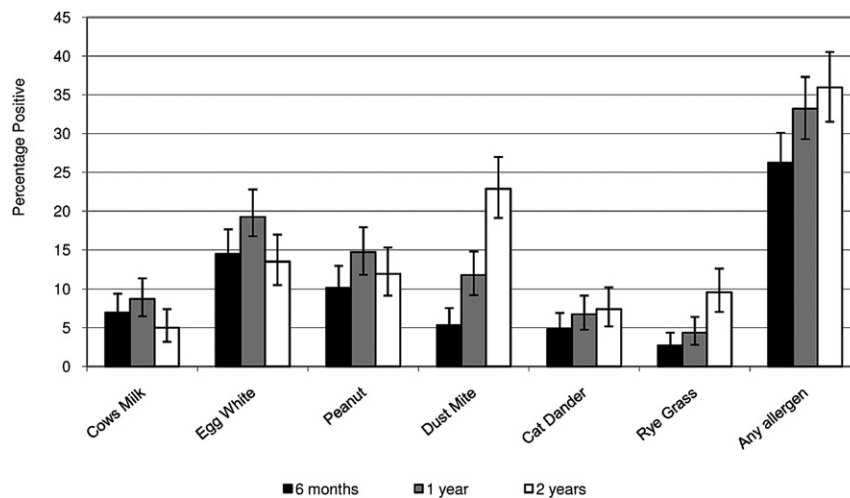


FIG 2. Prevalence of sensitization (and 95% CI) at age 6 months (n = 560), 1 year (n = 551), and 2 years (n = 459).

TABLE I. Associations between individual allergen sensitization profiles at age 1 year and wheeze at age 12 years (n = 352)

	No sensitization	Monosensitization*	Polysensitization†	Other sensitization‡
HDM				
Wheeze (n/N)	20% (48/235)	67% (10/15)	54% (15/28)	38% (28/74)
aOR (95% CI)	1	8.12 (2.13-31.0)	2.74 (1.10-6.86)	1.69 (0.91-6.86)
Rye grass				
Wheeze (n/N)	20% (48/235)	50% (1/2)	64% (7/11)	43% (45/104)
aOR (95% CI)	1	2.52 (0.15-43.0)	4.30 (1.10-16.8)	2.11 (1.20-3.70)
Cat dander				
Wheeze (n/N)	20% (48/235)	17% (1/6)	35% (7/20)	50% (45/91)
aOR (95% CI)	1	0 (not estimable)	1.58 (0.55-4.53)	2.80 (1.55-5.05)
Egg white				
Wheeze (n/N)	20% (48/235)	29% (5/17)	54% (27/50)	42% (21/50)
aOR (95% CI)	1	0.95 (0.28-3.23)	3.27 (1.60-6.67)	2.34 (1.13-4.85)
Cow's milk				
Wheeze (n/N)	20% (48/235)	50% (2/4)	58% (15/26)	41% (36/87)
aOR (95% CI)	1	7.32 (0.85-62.7)	4.25 (1.66-11.0)	2.02 (1.09-3.75)
Peanut				
Wheeze (n/N)	20% (48/235)	30% (3/10)	46% (19/41)	47% (31/66)
aOR (95% CI)	1	1.02 (0.20-5.25)	2.28 (1.04-4.98)	2.66 (1.38-5.14)

These results are derived from multiple logistic regression models adjusted for the relevant confounders.

*Participants sensitized only to the allergen of interest.

†Participants sensitized to the allergen of interest and at least 1 other allergen.

‡Participants monosensitized or polysensitized to allergens other than the allergen of interest.

associated with increased risk of wheeze at age 12 years compared with that seen in nonatopic children.

Furthermore, when the association of other sensitization with 12-year wheeze was examined, only the models that contained HDM generated strong evidence of an association between “other” sensitization and wheeze. The 1-year data are presented in Table I (2-year data are shown in Table E5).

The data were also analyzed without their inclusion to assess the robustness of the results to inclusion of early wheeze or eczema. The results (see Table E6 in this article’s Online Repository at www.jacionline.org) show that the overall associations were unchanged.

Children sensitized to HDM at age 1 and 2 years had 2.5 to 3 times the risk of mild wheeze and 6 to 13 times the risk of more severe wheeze at age 12 years when compared with nonsensitized children (see Table E7 in this article’s Online Repository at www.jacionline.org).

The association between HDM sensitization and wheeze severity did not differ between those monosensitized and polysensitized to HDM at 1 or 2 years. When grouped into categories of aero and food allergens, only sensitization to aeroallergens at ages 1 and 2 years was associated with an increased risk of wheeze at age 12 years (see Table E8 in this article’s Online Repository at www.jacionline.org).

Relationship between HDM sensitization at 1 and 2 years and wheeze at age 12 years by early wheezing and early eczema status

Children were at increased risk of wheeze at age 12 years if they had any (monosensitization or polysensitization) HDM sensitization (adjusted odds ratio: 1 year, 3.31 [95% CI, 1.59-6.91]; 2 years, 6.37 [95% CI, 3.48-11.66]).

TABLE II. Dust mite sensitization at 2 time points and 12-year wheeze

Dust mite sensitivity		Proportion of wheeze at 12 y (n)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
1 y	2 y	28% (88/315)				
–	–	19% (45/236)	1	–	1	–
+	–	22% (2/9)	1.21 (0.24-6.03)	.81	1.15 (0.20-6.69)	.88
–	+	48% (20/42)	3.86 (1.94-7.67)	<.001	4.52 (2.08-9.83)	<.001
+	+	75% (21/28)	12.73 (5.10-31.79)	<.001	10.50 (3.62-30.40)	<.001

OR, Odds ratio.

They were also at increased risk if they had doctor-diagnosed wheeze by 1 year (aOR, 2.43 [95% CI, 1.33-4.44]) or 2 years (aOR, 3.00 [95% CI, 1.65-5.45]) or eczema by 1 or 2 years (1-year aOR, 1.91 [95% CI, 1.09-3.34]; 2-year aOR, 1.96 [95% CI, 1.07-3.58]).

Among wheezy toddlers aged 1 year, HDM-sensitized children had almost 5 times the odds of wheeze at age 12 years when compared with wheezy children who were not HDM sensitized (aOR, 4.83 [95% CI, 1.45-16.09]). If a wheezy child was sensitized to HDM by 1 year, the probability of having wheeze at age 12 years was 75% (95% CI, 51% to 91%) compared with 36% (95% CI, 23% to 50%) for a wheezy child not sensitized to HDM.

Among eczematous toddlers aged 1 year, HDM-sensitized children had 2.7 times the odds of wheeze at age 12 years when compared with children with eczema who were not HDM sensitized (aOR, 2.70 [95% CI, 0.96-7.62]). If an eczematous child was sensitized to HDM by 1 year, the probability of wheeze at age 12 years was 67% (95% CI, 45% to 84%) compared with 35% (95% CI, 25% to 45%) for an eczematous child not sensitized to HDM.

The associations for children with wheeze and eczema at 2 years were concordant with the 1-year data (see Table E5). There was also an increased risk of wheeze at age 12 years for HDM-sensitized children aged 2 years who did not have early wheeze or eczema (aOR, 7.91 [95% CI, 2.29-27.32]).

HDM sensitization at 1 and 2 years and risk of wheeze

Table II presents the risk of wheeze at age 12 years after categorizing the children into 4 groups according to their HDM sensitization status by age 1 and 2 years. New-onset sensitization by 2 years or sensitization at both 1 and 2 years were both strong predictors of wheeze at age 12 years.

DISCUSSION

Our study showed HDM sensitization was associated with current wheeze at age 12 years in both monosensitized and polysensitized HDM-sensitized children. However, we were unable to derive any conclusions on similar associations in relation to other single allergens tested in this study because of the small number of positive SPT responses. Furthermore, when we considered children with sensitization profiles excluding HDM, we were unable to demonstrate an association with 12-year wheeze, suggesting that HDM might be a necessary form of sensitization to substantially increase the children's risk of wheeze. We also showed that HDM sensitization at both 1 and 2 years of age, especially among those with early-life wheeze

and eczema, was strongly associated with 12-year wheeze. We found no increased risk of wheeze at age 12 years for children who were transiently sensitized to HDM (HDM sensitized at age 1 year but not age 2 years). However, the numbers of children in this category were very small, and caution must be exercised in interpreting the association. Finally, two thirds to three quarters of wheezy children sensitized to HDM at 1 or 2 years had persistent wheeze at age 12 years. Similarly, more than two thirds of children with eczema sensitized to HDM at 1 or 2 years will have wheeze by age 12 years. Our findings suggest that testing for aeroallergen sensitization should be considered at 1 or 2 years of age in both wheezy and eczematous children.

It is important to identify children who have an increased risk of asthma at the earliest possible age. Strategies aimed to prevent asthma or improve its management²⁵ could then be focused on this group. Longitudinal cohort studies have previously shown that wheezy atopic children tend to have more persistent and severe asthma later in childhood.^{4,13} Many studies have defined childhood atopy by considering a battery of common allergens and not reporting single-allergen associations with atopic disease. This global assessment of atopy, irrespective of the particular allergen involved, is a crude measure, implicating all allergens when in fact some might not be relevant. Some studies have considered individual allergens. However, because many subjects are polysensitized, the associations between individual allergens and disease outcomes have not been clear. Hence we used a novel approach of investigating the effects of both monosensitization and polysensitization.

Atopic children are believed to exhibit an “allergic march,” commencing with early (up to around 2 years) sensitization to foods (typically egg and milk) and progressing to later aeroallergen sensitization.^{26,27} This aeroallergen sensitization is thought initially to be monosensitization, progressing to polysensitization by later childhood.^{15,28} Recently, other studies have challenged the accepted wisdom that aeroallergen sensitization testing is only useful in older children, finding a high prevalence of aeroallergen sensitization in 1- to 2-year-old children,²⁹ which was a strong predictor for atopic disease.^{10,30} Our findings agree with those of Sly et al,¹² who concluded that the “identification of an asthmatic child's atopic status in early life has practical clinical and prognostic implications.” Holt et al,³¹ in a population where HDM was the dominant allergen, had similar findings. They found specific IgE to HDM at age 2 years to be a strong predictor of persistent wheeze by age 5 years (12.7% risk). Their risks were further enhanced by the addition of data concerning severe lower respiratory tract infection.

Our findings are also similar to those of the Multi-Centre Allergy Study group,³² who found those with early (1-year) inhalant sensitization to be a high-risk group for asthma at age 7 years. However, their reported increase in asthma risk was limited to

those children whose mothers had a history of asthma. We did not find parental asthma or parental sensitization status at baseline to modify our observed associations. This discrepancy might relate to the nature of sampling of the 2 populations studied. The Multi-Centre Allergy Study is an allergy-enriched population-based study. In contrast, children within the MACS sample all have some degree of family history of allergic disease, which makes it difficult to find any interactions between family predisposition and the environment.

The Manchester Asthma and Allergy Study group³³ used a computer-generated Markov model to classify children into 5 phenotypes of sensitization: multiple early, multiple late, dust mite, non-dust mite, and no latent vulnerability. They related sensitization at age 1, 3, 5, and 8 years to respiratory outcomes at age 8 years and found differences in subsequent wheeze and asthma risk. Their “dust mite-only” group, which consisted of mostly children 3 years and older, cannot be compared directly with our 1- or 2-year-old dust mite monosensitized or polysensitized groups. In the current study we might be finding dust mite monosensitization before subsequent sensitizations occur. In both their and our research, early sensitization carries the greatest risk.

Ever since 1967, when Voorhorst et al³⁴ discovered that dust mites constitute the major allergen in household dust and suggested a role for HDM in the pathogenesis of asthma, debate has been fierce concerning the role of this mite and its highly allergenic feces. In 1992, Sporik et al³⁵ suggested there was enough evidence for HDM exposure to be implicated in the causality of asthma according to the criteria outlined by Hill.³⁶ Over the subsequent 20 years, the controversy has continued.^{37,38} Our findings address one of the concerns surrounding HDM and its possible role in the causality of asthma: that the association with HDM is demonstrated for monosensitized and polysensitized subjects.

A second area of concern raised is whether HDM sensitization might have been simply “a marker of exposure rather than a harbinger of disease.” To address this issue, we looked at children without wheeze aged 2 years who were sensitized to HDM and found that the odds of having wheeze at age 12 years were markedly increased when compared with the odds among children without HDM sensitization.

Whether HDM is causal in its relationship with asthma or whether it is an innocent bystander indicating only the presence of a genetic epithelial barrier deficiency^{39,40} or immune system dysfunction or whether another mechanism is responsible for the association, it still has one of the strongest and most consistent associations with asthma in various types of studies from different populations over different time periods and ages. Irrespective of the question of causality, this makes HDM sensitization an important marker of potentially lifelong and difficult asthma.

One limitation of this study is that participants are at high risk of allergic disease because of family history and therefore differ from the general population in the prevalence of atopic and allergic disease. Conducting studies in high-risk populations allows associations to be found from smaller numbers of subjects. The results from these studies would then be directly applicable to those with a similar risk, whereas these need to be further explored in populations who are not at a similar risk.

Another limitation of this analysis is the relatively small numbers of children sensitized at age 6, 12, and 24 months when examining wheeze at the 12-year follow-up. The retention rate at 12 years was 60%. Lack of a significant difference in baseline characteristics or early-life allergic disease in those

retained in the study when compared with those lost to follow-up suggests that there was minimal selective attrition. We investigated 6 locally relevant allergens for their associations with wheeze at age 12 years. The lack of association with monosensitization to allergens other than HDM might be related to the lack of power of the study. Evidence against this, however, is demonstrated by egg white monosensitization, which was the most prevalent form of monosensitization at age 1 year. Despite this, we were not able to demonstrate an association between egg white monosensitization and 12-year wheeze. Larger birth cohort studies would be needed to further analyze the relationships of allergens other than dust mite with allergic disease. Part of the difference between the 2 findings might be related to the differing allergen levels in the study countries.

One of the limitations of interpretation related to this study is the differing global prevalence of HDM exposure. In Australia HDM are present at high levels⁴¹ and are the most common cause of sensitization in the community. In Germany, however, where HDM levels are relatively low, HDM ranks third after grass and birch pollens.⁷ Thus another limitation of this work is that it is only applicable in areas where HDM is prevalent and the dominant aeroallergen. The role of HDM in other locations might be filled by other aeroallergens, including *Alternaria* species,⁴² grass, and birch pollens,⁷ depending on the local pattern of sensitization.

In conclusion, our findings have both public health and clinical implications. In areas of high HDM prevalence, HDM sensitization status could be used as one of a range of factors to identify children at high asthma risk for studies trialing asthma prevention strategies. HDM sensitization status in young children with eczema or early wheeze would inform discussions between physicians and parents about subsequent asthma risk. Assessment of HDM sensitization at age 1 year, 2 years, or both in high-risk children, especially those with early wheeze or eczema, might be a useful tool for identifying children at later risk for childhood asthma.

We thank John Thorburn, FRACP, for administration and recruitment; the Mercy Hospital Department of Obstetrics for participant recruitment; Christine Axelrad for data collection; and Anne Balloch for data management.

Clinical implications: HDM sensitization at age 1 or 2 years in wheezing or eczematous children can be used as a clinical tool to identify those at risk of asthma by age 12 years.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. *Allergy Asthma Proc* 2004;59:469-78.
2. Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multi-country cross-sectional surveys. *Lancet* 2006;368:733-43.
3. Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev* 2004;5:155-61.
4. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
5. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008;372:1058-64.
6. Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. *AI-lergy* 2005;60:1280-6.

7. Matricardi PM, Bockelbrink A, Keil T, Grüber C, Niggemann B, Hamelmann E, et al. Dynamic evolution of serum immunoglobulin E to airborne allergens throughout childhood: results from the Multi-Centre Allergy Study birth cohort. *Clin Exp Allergy* 2009;39:1551-7.
8. Ghunaim N, Wickman M, Almqvist C, Söderström L, Ahlstedt S, van Hage M. Sensitization to different pollens and allergic disease in 4-year-old Swedish children. *Clin Exp Allergy* 2006;36:722-7.
9. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414-22.
10. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szefer SJ, et al. The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Control Clin Trials* 2004;25:286-310.
11. Bierg-Bäcklund A, Perzanowski MS, Platts-Mills T, Sandström T, Lundbäck B, Rönmark E. Asthma during the primary school ages—prevalence, remission and the impact of allergic sensitization. *Allergy* 2006;61:549-55.
12. Sly PD, Boner AL, Björkstén B, Bush A, Custovic A, Eigenmann PA, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372:1100-6.
13. Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763-70.
14. Sporik R, Platts-Mills TAE. Allergen exposure and the development of asthma. *Thorax* 2001;56:ii58-63.
15. Fasce L, Tosca MA, Olcese R, Milanese M, Erba D, Ciprandi G. The natural history of allergy: the development of new sensitizations in asthmatic children. *Immunol Lett* 2004;93:45-50.
16. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112(suppl):S118-27.
17. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez FD, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
18. Almqvist C, Li Q, Britton WJ, Kemp AS, Xuan W, Tovey ER, et al. Early predictors for developing allergic disease and asthma: examining separate steps in the "allergic march." *Clin Exp Allergy* 2007;37:1296-302.
19. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy. Twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002;165:176-80.
20. Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. *Thorax* 2004;59:855-61.
21. Lowe AJ, Carlin JB, Bennett CM, Abramson MJ, Hosking CS, Hill DJ, et al. Atopic disease and breast-feeding—cause or consequence? *J Allergy Clin Immunol* 2006;117:682-7.
22. Lowe AJ, Hosking CS, Bennett CM, Carlin JB, Abramson MJ, Hill DJ, et al. Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis. *Clin Exp Allergy* 2007;37:1624-31.
23. Lowe A, Abramson M, Hosking C, Carlin J, Bennett C, Dharmage S, et al. The temporal sequence of allergic sensitization and onset of infantile eczema. *Clin Exp Allergy* 2007;37:536-42.
24. Hill D, Hosking C. Food allergy and atopic dermatitis in infancy: an epidemiological study. *Pediatr Allergy Immunol* 2004;15:421-7.
25. Bacharier LB, Phillips BR, Zeiger RS, Szefer SJ, Martinez FD, Lemanske RF Jr, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127-35, e8.
26. Nickel R, Kulig M, Forster J, Bergmann R, Bauer CP, Lau S, 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.
27. Illi S, von Mutius E, Lau S, Nickel R, Niggemann B, Sommerfeld C, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001;108:709-14.
28. Fasce L, Tosca MA, Baroffio M, Olcese R, Ciprandi G. Atopy in wheezing infants always starts with monosensitization. *Allergy Asthma Proc* 2007;28:449-53.
29. De Bilderling G, Mathot M, Agustsson S, Tuerlinckx D, Jamart J, Bodart E. Early skin sensitization to aeroallergens. *Clin Exp Allergy* 2008;38:643-8.
30. Brockow I, Zutavern A, Hoffmann U, Grübl A, Von Berg A, Koletzko S, et al. Early allergic sensitizations and their relevance to atopic diseases in children aged 6 years: results of the GINI study. *J Investig Allergol Clin Immunol* 2009;19:180-7.
31. Holt PG, Rowe J, Kusel M, Parsons F, Hollams EM, Bosco A, et al. Toward improved prediction of risk for atopy and asthma among preschoolers: a prospective cohort study. *J Allergy Clin Immunol* 2010;125:653-9, e7.
32. Illi S, Von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001;322:390-5.
33. Simpson A, Tan VYF, Winn J, Svensen M, Bishop CM, Heckerman DE, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010;181:1200-6.
34. Voorhorst R, Spieksma FTM, Varekamp H, Leupen MJ, Lyklema AW. The house-dust mite (*Dermatophagoides pteronyssinus*) and the allergens it produces: identity with the house dust allergen. *J Allergy* 1967;39:325-39.
35. Sporik R, Chapman MD, Platts-Mills TA. House dust mite exposure as a cause of asthma. *Clin Exp Allergy* 1992;22:897-906.
36. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.
37. Von Hertzen L, Hahtela T. Con: house dust mites in atopic diseases. Accused for 45 years but not guilty. *Am J Respir Crit Care Med* 2009;180:113-8.
38. Platts-Mills TA, Erwin EA, Heymann PW, Woodfolk JA. Pro: the evidence for a causal role of dust mites in asthma. *Am J Respir Crit Care Med* 2009;180:109-13.
39. Holgate ST. Has the time come to rethink the pathogenesis of asthma? *Curr Opin Allergy Clin Immunol* 2010;10:48-53.
40. Holgate ST, Roberts G, Arshad HS, Howarth PH, Davies DE. The role of airway epithelium and its interaction with environmental factors in asthma pathogenesis. *Proc Am Thorac Soc* 2009;6:655-9.
41. Tovey ER, Almqvist C, Li Q, Crisafulli D, Marks GB. Nonlinear relationship of mite allergen exposure to mite sensitization and asthma in a birth cohort. *J Allergy Clin Immunol* 2008;122:114-8, e5.
42. Stern DA, Lohman IC, Wright AL, Taussig LM, Martinez F, Halonen M. Dynamic changes in sensitization to specific aeroallergens in children raised in a desert environment. *Clin Exp Allergy* 2004;34:1563-9.

METHODS

Loss to follow-up analysis

Of the cohort, 60% had contributed data at the 12-year time point. [Table E1](#) on participant demographics presents data on participants who were either present or missing from each follow-up in terms of the proportions of baseline statistics. The only significant difference found was that the mothers of participants missing data at 6 months were less likely to be university educated.

Other demographics found to be not significantly different between those with and without data available at 12 years (details not included in the table) were as follows: reported milk or egg allergy in fathers and mothers, percentage of parents born in Australia, average weight of the infant at 4 weeks of age, any sibling atopy, cat ownership, first child in birth order, carpet

in the house, parental smoking, and whether the parents were receiving government benefits.

We also found that the odds of participants undergoing SPTs were not related to the result of previous SPTs ([Table E3](#)).

[Table E4](#) demonstrates no difference between the proportion of children sensitized in the whole cohort and in those with data available for inclusion into the analysis at 12 years.

All the participants were recruited on the basis of having at least 1 first-degree family member with a history of allergic disease. [Table E2](#) describes which family members were affected at baseline for the whole cohort and the subgroup analyzed at 12 years. There was no difference in the allergic heredity between the 2 groups.

TABLE E1. Baseline demographics of participants at each follow-up time point (%)

	Baseline	6 mo	1 y	2 y	12 y	6 mo Missing	1 y Missing	2 y Missing	12 y Missing
No. of participants	620	560	550	459	373	50	70	161	250
Sex (male/female)	51%/49%	51%/49%	51%/49%	52%/48%	53%/47%	48%/52%	49%/51%	48%/52%	49%/51%
Mother's age (y)	31.25	31.33	31.33	31.57	31.88	30.45	30.54	30.32	30.3
Father's age (y)	33.38	33.48	33.42	33.71	34.21	32.48	33.01	32.44	32.15
Mother is university educated (%)	58.71	61.43	60.98	63.18	62.97	33.33	40.00	45.96	52.40
Father is university educated (%)	61.10	62.48	63.14	63.02	60.98	55.63	44.29	48.33	61.29
Mother with eczema ever (%)	38.93	40.25	40.18	39.30	41.73	26.67	28.57	37.89	34.80
Father with eczema ever (%)	20.49	20.54	20.33	21.54	20.16	20.00	21.43	17.50	20.97
Mother with asthma ever (%)	43.30	42.75	43.09	42.79	43.90	48.43	45.71	44.72	42.40
Father with asthma ever (%)	25.69	25.77	25.27	26.37	27.25	25.00	30.00	23.75	23.39
Mother with hay fever ever (%)	60.58	60.11	60.73	59.61	58.81	65.00	60.00	63.35	63.20
Father with hay fever ever (%)	46.18	46.49	46.52	45.27	47.96	43.33	44.29	48.75	43.55
Any positive maternal SPT response (3 mm [%])	68.69	68.94	68.40	69.44	70.03	64.29	73.33	64.56	65.58
Any positive paternal SPT response (3 mm [%])	68.92	69.23	68.98	69.77	69.93	63.64	68.00	63.64	66.02

TABLE E2. Numbers of first-degree relatives with allergic disease

First-degree relatives with allergy at baseline	Percentage affected (n), whole cohort (n = 620)	Percentage affected (n), 12-y subgroup (n = 370)
Mother only	18 (109)	16 (60)
Father only	5 (30)	5 (18)
≥1 Sibling only	3 (21)	3 (12)
Mother and father	24 (147)	24 (89)
Mother and ≥1 sibling	19 (115)	18 (68)
Father and ≥1 sibling	9 (55)	10 (37)
Mother and father and ≥1 sibling	23 (143)	23 (86)

TABLE E3. Odds of attending next SPT if participant had any positive reaction on the previous SPT

Time point	Odds ratio	95% CI
1-2 y	1.22	0.55-2.73
2-3 y	1.55	0.62-3.88

TABLE E4. Prevalence of sensitization to 6 common allergens at 1 and 2 years in the whole cohort and in those who had data available at 12 years

Allergen	Proportion sensitized (% [n/N])			
	At 1 y		At 2 y	
	Total cohort	With data at 12 y	Total cohort	With data at 12 y
HDM	12% (65/551)	12% (43/352)	23% (105/459)	23% (71/315)
Cat dander	7% (37/551)	7% (26/352)	7% (34/459)	7% (23/315)
Rye grass	4% (24/551)	4% (13/352)	10% (44/459)	10% (30/315)
Peanut	15% (81/551)	14% (51/352)	12% (55/459)	12% (37/315)
Egg white	19% (106/551)	19% (67/352)	14% (62/459)	15% (47/315)
Cow's milk	9% (48/551)	9% (30/352)	5% (23/459)	5% (16/315)

TABLE E5. Odds of asthma at 12 years in children monosensitized and polysensitized to 6 allergens at age 2 years (n = 315)

	No sensitization	Monosensitization*	Polysensitization†	Other sensitization‡
HDM				
Asthma (n/N)	17% (33/198)	58% (19/33)	61% (23/38)	28% (13/46)
aOR (95% CI)	1	8.67 (3.37-22.31)	6.24 (2.72-14.31)	1.71 (0.74-3.93)
Rye grass				
Asthma (n/N)	17% (33/198)	0% (0/8)	64% (14/22)	47% (41/87)
aOR (95% CI)	1	0 (not estimable)	10.96 (3.70-32.47)	4.21 (2.26-7.84)
Cat dander				
Asthma (n/N)	17% (33/198)	0% (0/4)	68% (13/19)	45% (42/94)
aOR (95% CI)	1	0 (not estimable)	15.16 (4.55-50.59)	3.70 (2.01-6.82)
Egg white				
Asthma (n/N)	17% (33/198)	25% (2/8)	59% (23/39)	43% (30/70)
aOR (95% CI)	1	0.75 (0.12-4.68)	7.19 (3.43-15.06)	4.40 (2.21-8.72)
Cow's milk				
Asthma (n/N)	17% (33/198)	33% (1/3)	77% (10/13)	44% (44/101)
aOR (95% CI)	1	0 (not estimable)	16.68 (4.35-6.64)	3.93 (2.16-7.13)
Peanut				
Asthma (n/N)	17% (33/198)	0% (0/4)	55% (18/33)	46% (37/80)
aOR (95% CI)	1	0 (not estimable)	6.00 (2.75-13.10)	4.38 (2.31-8.32)

Variables included in each model include sex, parental asthma, and 4-week weight. Other confounders were included depending on the relevance to the allergen being examined and a change in odds ratio of greater than 10%.

*Participants sensitized only to the allergen of interest.

†Participants sensitized to the allergen of interest and at least 1 other allergen.

‡Participants monosensitized or polysensitized to allergens other than the allergen of interest.

TABLE E6. Odds ratio for current wheeze at 12 years by sensitization at 1 year to 6 common allergens with systematic exclusion of variables that might be on the causal pathway (early eczema and wheeze)

Category of sensitization	aOR (95% CI)	aOR (95% CI) without early eczema	aOR (95% CI) without early wheeze	aOR (95% CI) without either
HDM				
Monosensitized	7.92 (2.06-30.48)	8.16 (2.22-30.10)	10.38 (2.90-37.19)	10.63 (3.03-37.29)
Polysensitized	2.73 (1.08-6.91)	3.47 (1.44-8.40)	3.28 (1.35-7.93)	4.24 (1.81-9.96)
Not HDM	1.61 (0.8-3.06)	1.88 (1.02-3.48)	1.88 (1.03-3.43)	2.09 (1.16-3.78)
Cat dander				
Monosensitized	0	0	0	0
Polysensitized	1.51 (0.53-4.27)	1.75 (0.63-4.89)	1.79 (0.64-4.98)	2.13 (0.78-5.83)
Not cat dander	2.67 (1.47-4.86)	3.02 (1.69-5.42)	3.17 (1.80-5.60)	3.62 (2.08-6.30)
Rye grass				
Monosensitized	2.46 (0.13-43.57)	2.84 (0.17-47.06)	3.23 (0.15-68.91)	3.83 (0.22-67.87)
Polysensitized	4.14 (1.06-16.17)	4.63 (1.20-17.79)	5.80 (1.55-21.73)	6.30 (1.74-22.88)
Not rye grass	2.03 (1.14-3.63)	2.32 (1.32-4.07)	2.44 (1.41-4.21)	2.82 (1.66-4.79)
Peanut				
Monosensitized	1.02 (0.20-5.25)	0.98 (0.19-4.99)	1.06 (0.20-5.52)	1.02 (0.19-5.27)
Polysensitized	2.28 (1.04-4.98)	2.63 (1.22-5.65)	2.78 (1.34-5.79)	3.22 (1.56-6.64)
Not peanut	2.66 (1.38-5.14)	2.97 (1.56-5.66)	3.26 (1.74-6.10)	3.70 (2.01-6.83)
Egg white				
Monosensitized	0.95 (0.28-3.23)	1.15 (0.36-3.77)	1.27 (0.40-4.03)	1.52 (0.49-4.69)
Polysensitized	3.27 (1.60-6.67)	4.01 (2.00-8.03)	3.94 (1.97-7.90)	4.88 (2.48-9.61)
Not egg white	2.34 (1.13-4.85)	2.43 (1.18-4.98)	2.78 (1.38-5.59)	2.85 (1.43-5.68)
Cow's milk				
Monosensitized	7.29 (0.82-64.67)	6.94 (0.85-56.89)	6.93 (0.79-60.88)	6.55 (0.81-52.84)
Polysensitized	3.76 (1.48-9.51)	4.38 (1.75-10.96)	4.29 (1.78-10.34)	5.09 (2.13-12.15)
Not cow's milk	2.02 (1.09-3.74)	2.28 (1.25-4.15)	2.54 (1.42-4.56)	2.90 (0.99-2.38)

TABLE E7. Odds of wheeze or severe wheeze at 12 years compared with no wheeze if sensitized to HDM at 1 or at 2 years (n = 356 at 1 year and n = 319 at 2 years)

Age	HDM ⁺	No wheeze Percentage (n/N)	Mild wheeze		Severe wheeze	
			Percentage (n/N)	aOR (95% CI), <i>P</i> value	Percentage (n/N)	aOR (95% CI), <i>P</i> value
1 y	No	93 (236/255)	82 (51/62)	1	64 (25/39)	1
	Yes	7 (19/255)	17 (11/62)	2.54 (1.05-6.11), .04	36 (14/39)	6.28 (2.51-15.73), <.001
2 y	No	87 (200/231)	65 (33/51)	1	35 (13/37)	1
	Yes	13 (31/231)	35 (18/51)	2.94 (1.43-6.04), <.001	65 (24/37)	12.79 (5.35-30.58), <.001

TABLE E8. Allergens grouped in food allergen and aeroallergen categories and relationship to wheeze at 12 years

	Positive SPT response	Percentage (n/N)	Current wheeze, aOR (95% CI), <i>P</i> value
Aeroallergen			
1 y	No	24 (68/286)	1
	Yes	50 (33/66)	2.08 (1.05-4.11), .036
2 y	No	18 (41/222)	1
	Yes	51 (47/93)	4.17 (2.17-8.03), <.001
Food allergen			
1 y	No	23 (61/261)	1
	Yes	44 (40/91)	1.59 (0.85-2.97), .143
2 y	No	22 (55/250)	1
	Yes	51 (33/65)	1.84 (0.89-3.80), .100

Models include sex, 4-week weight, cat ownership, early wheeze, early eczema, maternal or paternal asthma; maternal or paternal food allergy and aeroallergen sensitization; or food allergen sensitization.