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Atopic dermatitis in a high-risk cohort: natural history, associated allergic outcomes, and risk factors

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ABSTRACT

Background: Atopic dermatitis (AD) is commonly associated with asthma and other atopic disorders in childhood.

Objective: To evaluate the natural history of AD and its association with other allergic outcomes in a high-risk cohort through the age of 7 years.

Methods: A total of 373 high-risk infants, who had undergone a randomized controlled trial with intervention measures for primary prevention of asthma applied during the first year of life, were assessed for asthma, AD, and allergic sensitization at 1, 2, and 7 years.

Results: The multifaceted intervention program did not reduce AD despite reducing the prevalence of asthma significantly. Sixty-two children (16.6%) had AD during the first 2 years (early-onset AD); of these, 26 continue to have AD at the age of 7 years (persistent), whereas 36 no longer had the disease (nonpersistent) at the age of 7 years. Twenty-three children (6.2%) developed AD only after the age of 2 years (late-onset AD). Early-onset AD, persistent or nonpersistent, was associated with increased risk of allergic sensitization to food allergens within the first 2 years of life and asthma diagnosis at year 7. However, only persistent AD was associated with an increased risk of other atopic diseases and allergic sensitization to food and aeroallergens at year 7. Late-onset AD was not associated with atopic diseases or allergic sensitization at year 7 with the exception of *Alternaria alternans*.

Conclusion: In this cohort of infants at high risk of asthma, early-onset persistent AD, which was highly associated with atopic sensitization, increased the risk of atopic diseases in later childhood and thus appears to be part of the atopic march.

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Introduction

Atopy was originally proposed to include asthma and allergic rhinitis in 1923; 10 years later, atopic dermatitis (AD) was added to this group of disorders and is often the first manifestation of the “allergic march.”¹ The prevalence of AD has increased in recent decades in tandem with the increased prevalence of asthma and other allergic disorders, yet only one-third of children with AD will develop asthma.² Therefore, one wonders, “What is the relationship of AD with allergic sensitization and other allergic disorders?”

“Is AD persistent in childhood once it developed?” “Are there personal characteristics or exposures that are predictive?”

We conducted a randomized, controlled, primary asthma prevention study in a high-risk cohort applying a multifaceted intervention program during the first year of life and found that it was effective in reducing asthma in the intervention group at the age of 7 years but had no effect on atopic dermatitis.^{3,4} In this article, we report on the natural history of AD and its association with allergic sensitization, asthma, and other allergic disorders in this high-risk cohort.

Materials and Methods

Study Participants

As previously described,^{3,4} study participants were identified before birth by recruiting mothers during the last trimester of pregnancy who were considered high risk (ie, having at least

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1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases [AD, allergic rhinitis, or food allergy]). Reasons for not participating included language difficulties, delivery of the infant before contact with study staff, and premature delivery. Families were randomly allocated to the multifaceted intervention group (n=279) or the control group (n=266). Children were assessed for various outcomes at the age of 1, 2, and 7 years.

The multifaceted intervention (avoidance of house dust mite, pets, and environmental tobacco smoke, encouragement of breastfeeding for at least 4 months, and delayed introduction of solid foods until at least 6 months of age) was implemented before birth and during the first year of life.

Study Protocol

Home visits were performed during the third trimester of the pregnancy and at intervals after childbirth. Dust samples were collected in households at the time of home visits and frozen until analysis. The dust samples were purified monoclonal antibodies against group 1 mite allergens, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Der p 1 and Der f 1), cat allergen (Fel d 1), and dog allergen (Can f 1).⁵⁻⁷

At the age of 1 and 2 years, children were assessed using a standard questionnaire modified from the International Study of Asthma and Allergic Disorders,⁸ had a physical assessment by a pediatric allergist, and allergy skin tests. At year 7, children were examined by the same allergist, who had no knowledge of the randomization and did not take part in the treatment of these children or their families, at each center. Allergists made a clinical diagnosis of AD, asthma, and allergic rhinitis based on a structured questionnaire and physical examination (each allergist using the definition below) without the knowledge of the skin prick test results. AD was defined as the presence of a pruritic rash on the face or extensor surface of the arms or legs and flexural lichenification at the time of examination.

Allergy skin tests were performed on the forearm epicutaneously with a prick lancet and the following allergens (Bayer Inc, Toronto, Ontario, Canada): egg, cow's milk, wheat, peanut, soy, house dust mite (*D pteronyssinus* and *D farinae*), cat, dog, grass, tree pollen, *Alternaria alternans* and *Cladosporium herbarum*. Histamine (1 mg/mL) was used as the positive control and saline as the negative control.

Statistical Analysis

Outcomes during the first 2 years of life included any wheeze in the last 12 months, recurrent wheeze (defined as 3 episodes of wheeze without apparent colds), rhinitis without colds (defined as ≥ 2 episodes of running nose and sneezing without apparent colds), food allergy (defined as a history of angioedema, urticaria, eczema, respiratory symptoms, or vomiting or diarrhea within 4 hours of ingestion of a recognized food allergen), and pediatric allergist-diagnosed AD. At year 7, outcomes were pediatric allergist-diagnosed AD, asthma, and allergic rhinitis and food allergy (defined as in year 1 or 2).

Risk factors associated with development of different types of AD were determined using logistic regression analyses with various types of AD as dependent variables compared with those without AD. Independent variables included were those found to be significant in the univariate analysis: race, city of residence, maternal history of asthma, and exposure to higher levels of dog allergen ($\geq 2 \mu\text{g/g}$) before the age of 2 years and at the age of 7 years. Sex and intervention were forced into the model.

To determine associations between various clinical outcomes and allergy skin test reactions and different type of AD, logistic regression analyses were performed with the various types of AD as

dependent variables with each of the clinical outcomes and allergy skin test results of interest as independent variables in separate models. Each model also included the following variables: race (white or other race), sex (male or female), first born (yes or no), socioeconomic status (mother with or without postsecondary education), city of residence (Vancouver or Winnipeg), maternal and history of AD or asthma (yes or no), house dust mite allergens (Der p1 and Der f 1), cat allergen (Fel d 1), dog allergen (Can f 1) (≥ 2 or $< 2 \mu\text{g/g}$) before the age of 2 years and dog allergen at the age of 7 years, exclusive breastfeeding for 4 months or more, and treatment allocation status.

Statistical analysis was performed using SPSS/PC version 10 (SPSS Inc, Chicago, Illinois) and Stata version 6.0 for Windows 8 (StataCorp, College Station, Texas).

Ethics committees of the University of British Columbia and the University of Manitoba approved the study (approval C00-0428. Parents signed informed consent forms.

Results

At 7 years of age, 380 (70%) of the original cohort returned for follow-up assessment, and 373 were examined on all 3 occasions. A total of 181 of these were in Vancouver and 192 were in Winnipeg. The number of families dropping out was not significantly different between the control and the intervention groups. Similar proportions of AD before the age of 24 months were found in those who returned for follow-up and those who did not (16.8% vs 13.2%, respectively; $P=.39$). Overall, allergen levels were significantly reduced by the intervention; dust mite levels were used as the proxy for dust control and were reduced by approximately one-third at 12 months.

Sixty-two of the 373 children (16.6%) had AD during the first 2 years of life (early-onset AD); of these, 36 (58.0%) did not have AD (early-onset, nonpersistent AD) at the age of 7 years, whereas 26 (41.9%) also had AD at 7 years of age (early-onset, persistent AD). Twenty-three children (6.1%) developed AD after the age of 2 years (late-onset AD) (Table 1). These diagnostic groups were not different in terms of intervention status.

As indicated in Table 1, significant differences were found between different AD groups in the proportion of whites (significantly lower among those with early AD than those without AD or with late-onset AD), the city of residence (Winnipeg more likely than Vancouver to have late-onset AD), and the proportion of mothers with a history of asthma (more likely among those with late-onset AD). The only exposure variable that was significantly different between different types of AD was exposure to dog allergen of $2 \mu\text{g/g}$ or greater before year 2 and at year 7. Logistic regression analysis revealed that residence in Winnipeg and exposure to cat allergen of $2 \mu\text{g/g}$ or higher before or at year 2 were associated with a reduced risk (adjusted odds ratio [OR], 0.37; 95% confidence interval [CI], 0.14–0.94; and adjusted OR, 0.23; 95% CI, 0.07–0.82, respectively) for early-onset, nonpersistent AD. Being a race other than white and residence in Winnipeg were associated with a significant increased risk (adjusted OR, 3.11; 95% CI, 1.14–8.48; and adjusted OR, 3.27; 95% CI, 1.17–9.17, respectively), whereas exposure to dog allergen at $2 \mu\text{g/g}$ or higher at year 7 was associated with a reduced risk (adjusted OR, 0.33; 95% CI, 0.11–0.99) of early-onset, persistent AD. The only risk factor associated with late-onset AD was residence in Winnipeg (adjusted OR, 10.0; 95% CI, 1.98–50.3).

Overall, 53% of children had positive skin test results to at least one of the tested allergens (any allergen), 27% tested positive to at least one of the tested food allergens (any food allergen), and 38% tested positive to at least one of the tested inhalant allergens (any inhalant allergen). Early-onset AD, irrespective of persistence, was significantly associated with positive skin test reaction to any food

Table 1

Comparison of baseline characteristics and exposures of children with different types of AD and those without AD

Variable	No AD, No. (%) (n=288; 77.2%)	Early-onset AD, No. (%)		Late-onset AD, No. (%) (n=23; 6.2%)	P value ^a
		Nonpersistent (n=36; 9.7%)	Persistent (n=26; 7.0%)		
White race	235 (81.6)	25 (69.4)	15 (57.7)	20 (87.4)	.01
Male sex	154 (53.5)	22 (61.1)	12 (46.2)	11 (47.8)	.64
First born	135 (46.9)	16 (61.1)	8 (30.8)	11 (47.8)	.46
Mother received postsecondary education	220 (76.4)	31 (86.1)	20 (76.9)	17 (73.9)	.60
Residence in Winnipeg	148 (51.4)	19 (25.0)	14 (53.8)	21 (91.3)	.001
Received intervention measures	155 (53.8)	18 (50.0)	14 (53.8)	11 (47.8)	.93
Maternal history of atopic dermatitis	99 (34.4)	19 (52.8)	12 (46.2)	9 (39.1)	.13
Maternal history of asthma	115 (39.9)	17 (47.2)	11 (42.3)	16 (69.6)	.046
Mother atopic (positive skin test result)	191 (66.3)	25 (69.4)	14 (53.8)	15 (65.2)	.59
Exposure before 2 years of age					
House dust mite allergen ≥ 2 $\mu\text{g/g}$	54 (18.8)	5 (13.9)	4 (15.4)	3 (13.0)	.80
Cat allergen Fel d 1 ≥ 2 $\mu\text{g/g}$	86 (29.9)	5 (13.9)	5 (19.2)	9 (39.1)	.09
Dog allergen Can f 1 ≥ 2 $\mu\text{g/g}$	153 (53.1)	16 (44.4)	9 (34.6)	17 (73.9)	.04
Exclusive breastfeeding for ≥ 4 mo	151 (52.4)	22 (61.1)	15 (57.7)	7 (30.4)	.120
Introduction of solids ≥ 4 mo	35 (12.3)	4 (11.1)	4 (15.4)	6 (26.1)	.29
Exposure during year 7					
House dust mite allergen ≥ 2 $\mu\text{g/g}$	115 (45.6)	13 (40.8)	9 (39.1)	9 (42.9)	.89
Cat allergen Fel d 1 ≥ 2 $\mu\text{g/g}$	169 (67.1)	17 (53.1)	14 (60.9)	13 (61.9)	.44
Dog allergen Can f 1 ≥ 2 $\mu\text{g/g}$	132 (52.4)	15 (46.9)	6 (26.1)	16 (76.2)	.01

Abbreviation: AD, atopic dermatitis.

^aDerived from χ^2 analysis of each type of AD versus no AD, for each variable. Bold indicates $P < .05$ for at least one type of AD versus no AD. See associated Results for details.

allergen at or before the age of 2 years; of the food allergens, reaction to egg was the most prevalent (Table 2). Early-onset, persistent AD was also significantly associated with positive skin test reaction to any allergen. Late-onset AD was not associated with any positive skin test reactivity at or before the age of 2 years. The different types of AD were not associated with wheeze, recurrent wheeze, rhinitis, or food allergy at that age.

Early-onset, nonpersistent AD was significantly associated with asthma but not with any other clinical outcome or positive skin test reactivity to any allergen at year 7 (Table 3). Early-onset, persistent AD was significantly associated with all 3 clinical diagnoses (asthma, allergic rhinitis, and food allergy) and with positive skin test reaction to any allergen, any food allergen, and any inhaled allergen. Late-onset AD was not significantly associated with any

clinical outcome or positive skin test reactivity to any allergen with the exception of *A alternans* at the age of 7 years. As the years progressed, those with AD were increasingly likely to have asthma at year 7 (7% of those with AD at year 1 had asthma at year 1, 19% of those with AD at year 1 had asthma at year 2, 21% of those with AD at year 2 had asthma at year 7, and 28% of those with AD at year 7 had asthma at year 7). Intervention status itself had no protective effect on those with AD in terms of later asthma development; near-equal proportions of children within the control and intervention groups, 10.3% and 10.6% respectively, developed AD on or before year 2 but remained free of asthma as of the age of 7 years. Sex differences in this relationship decreased as AD persistence increased: among those with no AD at any time point, 18% of males and 9% of females had asthma at the age of 7 years; among those

Table 2

Association between different clinical outcomes and skin test reactivity at or before the age of 2 years and different types of AD at year 7

Variable	No AD, No. (%)	Early-onset AD, No. (%) ^a				Late-onset AD ^a	
		Nonpersistent		Persistent		No. (%)	OR (95% CI)
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)		
Clinical outcome at or before year 2							
Wheeze in last 12 mo	106 (36.8)	12 (33.3)	0.83 (0.35–1.93)	10 (38.5)	1.10 (0.42–2.88)	8 (34.8)	0.67 (0.25–1.82)
Recurrent wheeze	39 (13.5)	6 (16.7)	1.31 (0.44–3.86)	2 (7.7)	0.34 (0.04–2.89)	6 (26.1)	1.52 (0.46–4.98)
Rhinitis	77 (26.7)	12 (33.3)	1.25 (0.53–2.97)	9 (34.6)	1.72 (0.60–4.93)	12 (52.2)	2.68 (0.97–7.41)
Food allergy	59 (20.6)	15 (41.7)	2.08 (0.87–4.94)	7 (26.9)	1.70 (0.62–4.66)	7 (30.4)	1.45 (0.49–4.26)
Positive skin test result at or before year 2							
Any allergy ^b	67 (23.4)	18 (51.4)	2.23 (0.99–4.99)	16 (61.5)	4.24 (1.65–10.9)	3 (13.0)	0.30 (0.06–1.37)
Any food allergen ^b	52 (18.2)	17 (48.6)	2.52 (1.11–5.74)	15 (57.7)	5.92 (2.23–15.7)	3 (13.0)	0.42 (0.09–1.96)
Any inhalant allergen $\neq$	8 (23.1)	3 (8.6)	2.97 (1.25–7.08)	1 (4.3)	4.06 (1.52–10.9)	5 (19.2)	0.27 (0.03–2.17)
Egg	39 (13.7)	15 (42.9)	2.97 (1.24–7.08)	10 (38.5)	4.06 (1.52–10.8)	2 (8.7)	0.27 (0.03–2.17)
Cow's milk	9 (3.2)	4 (11.4)	3.00 (0.64–13.9)	2 (7.7)	6.40 (1.03–39.7)	0 (0)	
Soy	5 (1.7)	2 (5.7)	2.64 (0.29–29.9)	1 (3.8)	4.02 (0.35–46.9)	0 (0)	
Wheat	5 (1.8)	2 (5.7)	1.70 (0.16–17.7)	1 (3.8)	5.05 (0.40–64.6)	0 (0)	
Peanut	18 (6.3)	7 (20.0)	2.24 (0.70–7.14)	11 (42.3)	16.0 (5.00–51.3)	2 (8.7)	1.18 (0.14–10.3)

Abbreviations: AD, atopic dermatitis; CI, confidence interval; OR, odds ratio.

^aAdjusted ORs (95% CIs) derived from polytomous regression analysis with the dependent variable being the 3 types of AD each vs no AD. Each clinical outcome or allergy skin test variable was forced into a separate model. Each model includes all baseline characteristics (race, sex, city of residence, mother's history of asthma), treatment allocation, exposure variables (house dust mite allergen [Der p1 and Der f1], cat allergen [Fel d1] dog allergen [Can f1] ≥ 2 $\mu\text{g/g}$ at or before year 2), and exclusive breastfeeding for 4 months or longer.

^bAny allergen includes cow's milk, egg white, soy, wheat, peanut, cat, dog, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, *Alternaria*, and *Cladosporium*. Any food allergen includes cow's milk, egg white, soy, wheat, and peanut. Any inhalant allergen includes cat, dog, house dust mite (*D pteronyssinus* and *D farinae*), cockroach, *Alternaria*, and *Cladosporium*.

Table 3

Association among various clinical outcomes, skin test reactivity at the age of 7 years, and different types of AD at the age of 7 years

Variable	No AD, No. (%) (n=228; 77.2%)	Early-onset AD, No. (%) ^a				Late-onset AD ^a (n=23; 6.2%)	
		Nonpersistent (n=36; 9.7%)		Persistent (n=26; 7.0%)		No. (%)	OR (95% CI)
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)		
Clinical outcome at year 7							
Asthma diagnosis	39 (13.5)	11 (30.6)	2.88 (1.07-7.74)	12 (46.2)	7.48 (2.53-22.2)	8 (34.8)	2.67 (0.90-7.86)
Allergic rhinitis	71 (24.7)	17 (47.2)	1.75 (0.77-3.94)	14 (53.8)	3.47 (1.34-8.99)	9 (39.1)	2.47 (0.86-7.11)
Food allergy	11 (3.8)	3 (8.3)	1.95 (0.35-10.9)	6 (23.1)	13.4 (2.94-61.4)	1 (4.3)	1.26 (0.16-11.7)
Positive skin test result at 7 years							
Any allergen	113 (40.6)	20 (55.6)	1.51 (0.67-3.38)	20 (80.0)	6.54 (1.96-21.8)	12 (52.2)	1.36 (0.50-3.67)
Any food allergen	23 (8.3)	8 (22.2)	2.60 (0.89-7.62)	11 (44.0)	8.46 (2.83-25.3)	5 (21.7)	2.51 (0.74-8.52)
Any inhalant allergen	112 (40.3)	20 (55.6)	1.52 (0.67-3.41)	20 (80.0)	6.56 (1.96-21.9)	12 (52.2)	1.36 (0.50-3.69)
<i>Alternaria</i>	31 (11.2)	3 (8.3)	0.44 (0.05-3.74)	10 (40.0)	5.27 (1.41-19.6)	8 (34.8)	3.06 (1.04-9.02)
<i>Cladosporium</i>	18 (6.5)	3 (8.3)	0.65 (0.07-5.77)	8 (32.0)	6.30 (1.58-25.1)	4 (17.4)	1.78 (0.46-6.91)
House dust mite	43 (15.5)	5 (13.9)	0.49 (0.13-1.82)	8 (32.0)	1.78 (0.60-5.31)	5 (21.7)	1.02 (0.30-3.48)
Cat allergen	43 (15.5)	8 (22.2)	1.16 (0.39-3.48)	10 (40.0)	3.94 (1.31-11.9)	7 (30.4)	1.77 (0.60-5.29)
Dog allergen	23 (8.3)	5 (13.9)	1.46 (0.62-3.42)	8 (32.0)	0.33 (0.10-1.06)	5 (21.7)	1.33 (0.41-4.27)

Abbreviations: AD, atopic dermatitis; CI, confidence interval; OR, odds ratio.

^aAdjusted ORs (95% CIs) derived from polytomous regression analysis with the dependent variable being each of the 3 types of AD vs no AD. Each clinical outcome or allergy skin test variable was forced into a separate model. Each model includes all baseline characteristics (race, sex, city of residence, mother history of asthma), treatment allocation, exposure variables (house dust mite allergen [Der p1 and Der f1], cat allergen [Fel d1], dog allergen [Can f1] ≥ 2 $\mu\text{g/g}$ at or before year 2), and exclusive breastfeeding lasting 4 months or longer.

with early AD, 36% of males and 21% of females had asthma at the age of 7 years; among those with persistent AD, 50% of males and 43% of females had asthma at the age of 7 years. However, this trend was not statistically significant.

Discussion

We were interested in dissecting the temporal dynamics of AD in particular because overall AD was less remediable than asthma on application of our study's multifaceted intervention; it is possible that deeper understanding of the natural history of AD will help us better envision potentially effective remediation strategies for AD. In this high-risk cohort, most children (two-thirds) who had AD developed it early, during the first 2 years of life. Only 42% of children with early-onset AD had persistent disease at the age of 7 years. Our findings in this aspect are consistent with those of the German Multicenter Allergy Study, which reported 37% of their children who had early-onset AD continued to have AD at year 7.⁹ On the other hand, a Swedish study found as high as 91% of children with early-onset AD went into remission at the age of 8 years.¹⁰

One-third of the children with AD in this high-risk cohort developed the disease after the age of 2 years. These children with late-onset AD were mostly nonatopic and were not associated with increased risk of asthma or allergic rhinitis at the age of 7 years even though there was a trend. This finding may be because those with late-onset AD are simply earlier in their allergic march. Children with early-onset AD (persistent and nonpersistent) were atopic patients with positive skin test reactions to any food allergen before or at the age of 2 years. Those with persistent AD also had significantly increased risks of allergic sensitization to inhaled allergens and a diagnosis of asthma, allergic rhinitis, or food allergy at the age of 7 years. These findings concurred with reports in the literature that children with early-onset AD usually developed other atopic diseases later in childhood^{11,12} and are also consistent with allergic (or atopic) march as described by Spergel and Paller.¹ However, eczema that commenced in the first 6 months of life was less closely associated with asthma than was eczema that commenced in later life, in contradiction to a previous report.¹³ Finally, we note that nonpersistent AD was not associated with asthma, rhinitis, or food allergy at 2 years of age and was associated only with asthma at 7 years of age. On the basis of this pattern compared with that of patients with persistent AD, one may

speculate that the allergic march further drives persistence of AD. However, only further investigations at a later age, which we intend to perform with this cohort, will be able to test these hypotheses.

It is well known that early AD is associated with positive skin test reactivity to food allergens^{10,11,14} and inhaled allergens.^{15–18} The European multicenter study found that food and inhaled allergens are able to elicit eczematous skin reactions after patch testing, and the results correlated well with clinical history.¹⁹ Uncontrolled clinical trials found that removal of patients from their usual environments led to clinical improvement in their skin conditions.^{20–22} In our high-risk cohort, skin test positivity to house dust mite at year 7 was not associated with any type of AD. On the other hand, we found positive skin test reactions at year 7 to cat allergen and fungal allergens, *A alternans* and *C herbarum*, were significantly associated with persistent AD, whereas positive skin test reaction to *A alternans* was significantly associated with late-onset AD. These 2 fungal allergens, present mostly outdoors, are also found indoors.²³ Whether AD is part of the manifestation of allergic sensitization to inhaled allergens or allergic sensitization to inhaled allergens is the result of increased dermal absorption of these allergens by AD lesions is not clear. The strong association between sensitization to inhaled allergens and persistent AD, however, may well support the dermal route of sensitization and the importance of defects in filaggrin in the pathogenesis of AD.²⁴ In fact, recent studies have reported that the loss-of-function mutations in the gene encoding the skin barrier protein filaggrin (*FLG*) confer major susceptibility to AD and asthma.^{25,26} This genetic predisposition for atopic diseases may explain the atopic march in these children. Genetics may also explain, in part, the imperfect and variable prediction of allergic disease using nongenetic characteristics of high-risk among different study populations.²⁷

The effect of pet ownership on atopic diseases is controversial, with some studies showing an increased risk and others a protective effect, depending on the timing of exposure and the atopic predisposition of the children.²⁸ In this high-risk cohort, early exposure to higher levels of cat allergen (≥ 2 $\mu\text{g/g}$) reduced the risk of early-onset nonpersistent AD, whereas exposure to higher levels of dog allergen before the age of 2 years and at year 7 had a protective effect on early-onset persistent AD. Our findings are consistent with those in the literature that report that exposure to furred pets in infancy is associated with changes in immune development, leading to protection against allergic sensitization and atopic dermatitis.^{29,30} Although it is controversial whether the

existing literature is sufficient to support a specific recommendation for the adoption of pets in infancy, our work may be considered in future efforts to synthesize such literature in formulating such a recommendation.

A limitation of our study is that we do not precisely specify the biological onset of asthma because the related pathophysiologic findings precede the physician diagnosis of asthma. Furthermore, this high-risk cohort is relatively small, and the follow-up was incomplete. However, it is one of the most carefully conducted prospective studies in which phenotyping of asthma and AD was performed by pediatric allergists and the children's environment so carefully documented in early life. The reader is further cautioned that the AD outcomes in the high-risk group described in this study may not be comparable with those of other studies whose definition of high risk differed from ours (infants with at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases [AD, seasonal or perennial allergic rhinitis, or food allergy]).

In conclusion, in this cohort at high risk of asthma, early AD is not a persistent illness because more than half of children with the illness went into remission by the age of 7 years. Early-onset AD, regardless of persistence, was associated with sensitization to food allergens before 2 years and asthma at 7 years, but only those with persistent AD were at increased risk of immunologic sensitization to inhaled allergens, clinical food allergy, and allergic rhinitis at 7 years of age.

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