Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study

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Background: The atopic march describes the progression from atopic dermatitis during infancy to asthma and allergic rhinitis in later childhood. In a Canadian birth cohort we investigated whether concomitant allergic sensitization enhances subsequent development of these allergic diseases at age 3 years.

Methods: Children completed skin prick testing at age 1 year. Children were considered sensitized if they produced a wheal 2 mm or larger than that elicited by the negative control to any of 10 inhalant or food allergens. Children were also assessed for atopic dermatitis by using the diagnostic criteria of the UK Working Party. At age 3 years, children were assessed for asthma, allergic rhinitis, food allergy, and atopic dermatitis. Data from 2311 children were available.

Results: Atopic dermatitis without allergic sensitization was not associated with an increased risk of asthma at age 3 years after adjusting for common confounders (relative risk [RR], 0.46; 95% CI, 0.11-1.93). Conversely, atopic dermatitis with allergic sensitization increased the risk of asthma more than 7-fold (RR, 7.04; 95% CI, 4.13-11.99). Atopic dermatitis and allergic sensitization had significant interactions on both the additive (relative excess risk due to interaction, 5.06; 95% CI, 1.33-11.04) and multiplicative (ratio of RRs, 5.80; 95% CI, 1.20-27.83) scales in association with asthma risk. There was also a positive additive interaction between atopic dermatitis and allergic sensitization in their effects on food allergy risk (relative excess risk due to interaction, 15.11; 95% CI, 4.19-35.36).

Conclusions: Atopic dermatitis without concomitant allergic sensitization was not associated with an increased risk of asthma. In combination, atopic dermatitis and allergic sensitization had strong interactive effects on both asthma and food allergy risk at age 3 years. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Atopic march, asthma, allergic rhinitis, food allergy, atopic dermatitis, birth cohort, additive interaction, multiplicative interaction*

Many children have pruritic, chronic inflammatory skin disorders during the first year of life, variably called atopic dermatitis or eczema, affecting sleep and quality of life.[1,2] An estimated 10% to 20% of children worldwide have atopic dermatitis.[3] Interestingly, studies show that approximately two thirds of children given a diagnosis of classical atopic dermatitis are, in fact, not sensitized to allergens.[4] As a result, *atopic dermatitis* is a commonly used misnomer, prompting the World Allergy Organization to recommend in 2003 that the terms *atopic dermatitis* and *atopic eczema* be applied exclusively to atopic patients.[5]

The atopic march refers to the natural history of atopic manifestations, with a typical progression from atopic dermatitis to asthma and allergic rhinitis.[6] Several studies hypothesize a causal pathway,[6-11] including documentation of atopic comorbidities during a clinical trial of atopic dermatitis treatment[10] and a large retrospective study of atopic comorbidities based on health care provider diagnostic data.[11] Other studies suggest that the atopic march might oversimplify the natural history of childhood atopy.[12,13]

The connection between atopic dermatitis and asthma might be skin barrier dysfunction, specifically loss-of-function variants of the gene encoding filaggrin (*FLG*), a skin matrix protein that promotes aggregation of keratin filaments.[14] In the German Multicenter Allergy Study birth cohort *FLG* variants were highly

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Abbreviations used
aRR: Adjusted relative risk
CHILD: Canadian Healthy Infant Longitudinal Development
FLG: Filaggrin
RERI: Relative excess risk due to interaction
RR: Relative risk

predictive of asthma in children with eczema and sensitization to food allergens.[15] In the Isle of Wight birth cohort, allergic sensitization and eczema status were found to be independent effect modifiers of the relationship between *FLG* variants and asthma but not rhinitis.[16]

Because *FLG* genotyping is not typically available in clinical management,[9] alternative prognostic approaches for children with atopic dermatitis are needed. In particular, there has been a call for well-conducted longitudinal studies that compare differences in prognosis between sensitized and nonsensitized children.[4] This is especially important considering the global epidemic of asthma, allergy, and allergic rhinitis.[17] The Canadian Healthy Infant Longitudinal Development (CHILD) study[18] is a multicenter prospective birth cohort established to determine the root causes of allergic diseases in children. Here we investigated whether allergic sensitization enhances associations between atopic dermatitis in infancy with subsequent allergic diseases, including asthma, allergic rhinitis, food allergy, and persistent atopic dermatitis.

METHODS

Study design and cohort

The CHILD study is a multicenter longitudinal cohort of 3495 Canadian infants recruited during pregnancy and followed from birth to age 5 years. Child health questionnaires and clinical assessments of allergic diseases were conducted at regular intervals, including 1 and 3 years of age. The current analysis involves 2311 children who had complete data for clinical assessment at age 1 and 3 years, and all required adjustment variables.

Assessment of allergic sensitization

At age 1 year, children were administered epicutaneous skin tests to a battery of 6 inhalant (*Alternaria alternata*, cat hair, dog epithelium, house dust mites [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], and German cockroach) and 4 food (cow's milk, egg white, peanut, and soybean) allergens. As in our previous epidemiologic studies,[19-24] children were considered sensitized if they produced a wheal 2 mm or larger than that elicited by the negative control (glycerin) to at least 1 of the allergens. In cases in which skin tests were refused, some parents provided the results of external tests performed by other physicians, which were used to determine atopic status.

Assessment of allergic diseases

At the clinical assessment at age 1 year, the CHILD study physicians (A.B.B., P.J.M., P.S., and S.E.T.; all experienced pediatricians specializing in allergy and asthma) or other highly trained health care professional under their direction answered the question "Does this child meet the criteria for diagnosis of atopic dermatitis?" with the options "yes" or "no." These criteria were derived from the UK Working Party document,[25] namely an itchy skin condition with 1 or more of the following: a history of involvement of the skin creases of elbows, behind the knees, in front of the ankles, or around the neck; a history of general dry skin in the last year; or visible flexural eczema or eczema involving the cheeks/foreheads and outer limbs.

At the clinical assessment at age 3 years, the CHILD study physician or health care professional undertook a careful assessment of the clinical history during the past year and then responded to the following question: "In your opinion, does the child have any of the following: asthma, allergic rhinitis, food allergy, atopic dermatitis (Yes/Possible/No)?" Children were considered to have the outcome only if the response was definitively "yes." All diagnoses were reviewed by the study physician.

Covariate measures

Covariates considered in the study were child sex, study center, first-born status, ethnicity, household income, parental atopy based on skin prick testing, and parental self-reported history of allergic diseases (asthma, allergic rhinitis, food allergy, or atopic dermatitis). Parental atopy and disease history were considered positive if at least 1 of the parents had a positive test response (≥2-mm wheal to any allergen) or reported an allergic history. When data were missing for 1 parent and the other parent had a negative result, the child was considered not to have a parental history for atopy or allergic disease. Parental ethnicity was used to define child ethnicity, with a child considered white if at least 1 parent was white.

Statistical analysis

The relationship between atopic dermatitis and allergic sensitization at age 1 year with the outcomes of allergic disease at age 3 years was assessed by using multivariable modified Poisson regression.[26] Relative risks (RRs) and adjusted relative risks (aRRs) were calculated for both unadjusted and adjusted (for child's sex, study center, ethnicity, parental history of allergic diseases, and pet ownership) effects of atopic dermatitis and allergic sensitization at age 1 year. Interaction between atopic dermatitis and allergic sensitization was assessed in both the multiplicative and additive scales.[27,28] Multiplicative interaction was assessed by adding an interaction term to the adjusted and unadjusted model.

Relative excess risk due to interaction (RERI) was used to assess for additive interaction, in which an $RERI_{RR}$ value of greater than 0 indicates a positive additive interaction and an $RERI_{RR}$ value of less than 0 indicates a negative additive interaction. Calculation of 95% CIs was done by using the methods of variance estimates recovery.[29] The comparison group consisted of nonsensitized children without atopic dermatitis at age 1 year.

Two sensitivity analyses were undertaken. In the first analysis the definition of sensitization was changed from a wheal size of 2 mm or greater to a wheal size of 3 mm or greater, which is traditionally regarded as indicating clinically relevant sensitization. In the second analysis we excluded children with reported food allergy at age 3 months, 6 months, and/or 1 year to determine whether food allergy at age 3 years was simply a continuation of food allergy from early childhood.

All analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Study population

At 1 year, among 2311 children eligible for this analysis, 317 (13.7%) were sensitized, with 252 (10.9%) sensitized to 1 or more food allergens and 95 (4.1%) sensitized to 1 or more inhalant allergens (Table I; for data on full cohort, see Table E1 in this article's Online Repository at www.jacionline.org). The most frequent food sensitization was to egg white (7.4%), followed by peanut (5.1%) and cow's milk (1.9%). At the 1-year clinic visit, 265 children were determined to have atopic dermatitis (11.5%). Considering allergic sensitization and atopic dermatitis, 221 (9.6%) children were sensitized but did not have atopic dermatitis, 169 (7.4%) had atopic dermatitis but were not sensitized, 96 (4.2%) had both, and 1825 (78.9%) had neither.

At the 3-year clinic visit, 81 (3.5%) of these 2311 children were considered to have definite asthma (53 received oral or inhaled

TABLE I. Characteristics of the study sample (n = 2311)

Demographics	No. (%)
Sex	
Male	1238 (53.6)
Female	1073 (46.4)
Study center	
Edmonton	480 (20.8)
Toronto	461 (20.0)
Vancouver	558 (24.2)
Winnipeg	812 (35.1)
Parental atopic status	
≥1 Positive skin test result	1855 (80.3)
Negative results on all skin tests	456 (19.7)
Child atopic status at age 1 y	
Any sensitization	317 (13.7)
Any food allergen	252 (10.9)
Peanut	118 (5.1)
Milk	43 (1.9)
Egg white	171 (7.4)
Any inhalant allergen	95 (4.1)
Nonsensitized	1994 (86.3)
Atopic dermatitis at age 1 y	
Yes	265 (11.5)
No	2046 (88.5)
Allergic sensitization and atopic dermatitis at age 1 y	
Sensitized only	221 (9.6)
Atopic dermatitis only	169 (7.4)
Both	96 (4.2)
Neither	1825 (78.9)
Ethnicity	
Both white parents	1534 (66.5)
White and other	428 (18.5)
Both parents nonwhite	346 (15.0)
Mother's ethnicity	
First Nation	77 (3.3)
Southeast Asian	298 (12.9)
South Asian	50 (2.2)
Black	41 (1.8)
White	1742 (75.6)
Other	96 (4.2)
Unknown	2 (0.09)
Father's ethnicity	
First Nation	80 (3.5)
Southeast Asian	243 (10.5)
South Asian	73 (3.2)
Black	62 (2.7)
White	1755 (76.0)
Other	86 (3.7)
Unknown	11 (0.5)
Atopic status at age 3 y	
Any sensitization	328 (14.6)
Any food allergen	133 (5.9)
Peanut	92 (4.1)
Milk	28 (1.3)
Egg white	55 (2.5)
Any inhalant allergen	215 (9.6)
Nonsensitized	1924 (85.4)
Atopic dermatitis at age 3 y	
Yes	250 (10.8)
No	2061 (89.2)
Diagnosed asthma at age 3 y	
Yes	81 (3.5)
No	2230 (96.5)
Allergic rhinitis at age 3 y	
Yes	54 (2.3)
No	2257 (97.7)
Food allergy at age 3 y	
Yes	103 (4.5)
No	2208 (95.6)
Household income	
$0-$49,999	310 (14.8)
$50,000-$99,999	830 (40.0)
$100,000-$149,999	554 (26.6)
>$150,000	392 (18.8)

Parental history of allergic diseases	Mother	Father
Any allergic disease	1811 (79.0)	1418 (70.7)
Atopic dermatitis (eczema)	1433 (62.6)	933 (46.5)
Allergic rhinitis	1142 (49.8)	973 (48.5)
Food allergy	509 (23.4)	348 (17.6)
Asthma	514 (22.5)	396 (19.8)
No parental history	482 (21.0)	589 (29.4)

corticosteroids in the last year), 54 (2.3%) were considered to have allergic rhinitis, 103 (4.5%) were considered to have food allergy, and 250 (10.8%) were considered to have atopic dermatitis.

Associations with asthma at age 3 years

The strongest interaction between atopic dermatitis and sensitization was observed for diagnosed asthma. Assessed independently, both atopic dermatitis (ignoring sensitization) and sensitization (ignoring atopic dermatitis) at age 1 year independently increased the risk of asthma at age 3 years (aRR, 2.23 [95% CI, 1.36-3.67] and 4.37 [95% CI 2.85-6.69], respectively) after adjustment for child's sex, ethnicity, study center, pet ownership, parental atopy, and parental history of any allergic diseases (Table II). However, children with atopic dermatitis without allergic sensitization were not at an increased risk (aRR, 0.46; 95% CI, 0.11-1.93) compared with the reference group of nonsensitized children without atopic dermatitis, whereas children with both atopic dermatitis and allergic sensitization had a 7-fold increased risk of asthma (aRR, 7.04; 95% CI, 4.13-11.99) after adjustment as above (Table III). Atopic dermatitis and sensitization had a significant positive interaction on both the multiplicative (RR ratio, 5.80; 95% CI, 1.20-27.83) and additive (RERI, 5.06; 95% CI, 1.33-11.04) scales (Table III) after adjustment for covariates. When sensitization was further categorized as food or inhalant sensitization, food sensitization and atopic dermatitis had a significant positive interaction on the risk of asthma at age 3 years but only on the additive scale, whereas inhalant sensitization did not (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org).

Associations with allergic rhinitis at age 3 years

Among all children, atopic dermatitis (ignoring sensitization) at age 1 year significantly increased the risk of allergic rhinitis at

TABLE II. Effects of atopic dermatitis and sensitization at age 1 year on subsequent allergic outcomes at age 3 years (n = 2311)

	Atopic dermatitis at age 1 y (n = 265)			Allergic sensitization at age 1 y (n = 317)		
Outcome at age 3 y	No. of events at age 3 y (%)*	Unadjusted RR (95% CI)	aRR (95% CI)†	No. of events at age 3 y (%)*	Unadjusted RR (95% CI)	aRR (95% CI)†
Asthma	19 (7.17)	2.37 (1.44-3.89)‡	2.23 (1.36-3.67)‡	31 (9.78)	3.90 (2.53-6.01)‡	4.37 (2.85-6.69)‡
Allergic rhinitis	23 (8.68)	5.73 (3.39-9.67)‡	4.44 (2.59-7.63)‡	25 (7.89)	5.42 (3.22-9.14)‡	4.85 (2.84-8.27)‡
Food allergy	46 (17.36)	6.23 (4.32-9.00)‡	4.61 (3.02-7.05)‡	77 (24.29)	18.63 (12.14-28.59)‡	16.47 (10.64-25.49)‡
Atopic dermatitis	93 (35.1)	4.57 (3.66-5.71)‡	3.79 (2.98-4.83)‡	78 (24.61)	2.85 (2.24-3.63)‡	2.43 (1.89-3.12)‡

*Percentage of events calculated among children who had atopic dermatitis/sensitization at 1 year of age.
†Adjusted for ethnicity, study center, child's sex, pet ownership, parental atopy, and parental history of any allergic diseases. Numbers for adjusted models are lower because of missing data required for adjustment. For unadjusted data see Table E4 in this article's Online Repository at www.jacionline.org.
‡Statistically significant at the .05 level.

age 3 years (aRR, 4.44; 95% CI, 2.59-7.63), as did sensitization (ignoring atopic dermatitis) at age 1 year (aRR, 4.85; 95% CI, 2.84-8.27), after adjustment for covariates (Table II). Compared with nonsensitized children without atopic dermatitis, atopic dermatitis alone increased the risk of allergic rhinitis more than 4-fold (RR, 4.53; 95% CI, 2.13-9.63), sensitization alone increased the risk of allergic rhinitis more than 5-fold (RR, 5.35; 95% CI, 2.70-10.60), and atopic dermatitis with sensitization increased the risk of allergic rhinitis at age 3 years more than 11-fold (aRR, 11.75; 95% CI, 5.73-24.12) in adjusted analyses (Table III). There was no evidence of an interactive effect (RR ratio, 0.49 [95% CI, 0.17-1.36] and RERI, 2.62 [95% CI, −5.48 to 14.05]; Table III).

Associations with food allergy at age 3 years

Atopic dermatitis at age 1 year was associated with an increased risk of food allergy at age 3 years (aRR, 4.61; 95% CI, 3.02-7.05), whereas sensitization at age 1 year was an even stronger risk factor (aRR, 16.47; 95% CI, 10.64-25.49) after adjustment for covariates (Table II). The presence of both atopic dermatitis and sensitization at age 1 year was associated with a greatly increased risk of food allergy at age 3 years (aRR, 33.79; 95% CI, 18.89-60.47) relative to the reference group of nonsensitized children without atopic dermatitis (Table III). The presence of sensitization and atopic dermatitis had a highly significant positive interaction on the additive scale (RERI, 15.11; 95% CI, 4.19-35.36) but not on the multiplicative scale (RR ratio, 0.77; 95% CI, 0.29-2.03) after adjustment for covariates (Table III). Specifically, sensitization to food allergens and atopic dermatitis had significant additive interactive effects on the risk of food allergy at age 3 years; sensitization to inhalant allergens and atopic dermatitis did not interact significantly (see Table E3). A sensitivity analysis revealed that excluding children with reported food allergy at age 3 months, 6 months, and/or 1 year did not change the effect of atopic dermatitis and sensitization at age 1 year on food allergy at age 3 years (data not shown but available on request).

Associations with atopic dermatitis at age 3 years

Within the study sample, atopic dermatitis at age 1 year greatly increased the risk of atopic dermatitis at age 3 years (aRR, 3.79; 95% CI, 2.98-4.83; Table II). Any sensitization at age 1 year also increased the risk of atopic dermatitis at age 3 years, although to a somewhat lesser extent (aRR, 2.43; 95% CI, 1.89-3.12), after adjustment for covariates. Compared with the reference group of nonsensitized children without atopic dermatitis, sensitized children with atopic dermatitis at age 1 year exhibited a 6-fold increased risk of atopic dermatitis at age 3 years (aRR, 6.00; 95% CI, 4.36-8.23; Table III). However, there was no evidence of an interactive effect between sensitization and atopic dermatitis on the risk of atopic dermatitis either on the multiplicative (RR ratio, 0.89; 95% CI, 0.54-1.45) or additive (RERI, 1.44; 95% CI, −0.61 to 3.81) scale (Table III).

Unadjusted values can be found in Table E4 in this article's Online Repository at www.jacionline.org. The sensitivity analysis performed with a 3-mm or greater wheal cutoff instead of a 2-mm or greater cutoff to define sensitization yielded similar results that remained consistent across all outcomes (see Table E5 in this article's Online Repository at www.jacionline.org).

Fig 1 shows the additive interactions for all allergic outcomes at age 3 years.

DISCUSSION

Atopic dermatitis without concomitant allergic sensitization was not associated with an increased risk of asthma at age 3 years, whereas atopic dermatitis with allergic sensitization increased the risk of asthma more than 7-fold. The presence of both atopic dermatitis and sensitization had positive additive and multiplicative interactions in their effects on asthma. There was a strong positive additive interaction between atopic dermatitis and sensitization in the risk for food allergy, although interaction in the multiplicative scale was not significant. In other words, for asthma, the combined effect of atopic dermatitis and sensitization was greater than the sum of or the product of their individual effects. For food allergy, the combined effect of atopic dermatitis and sensitization at age 1 year was greater than the sum of their individual effects.

Based on the Isle of Wight birth cohort, Ziyab et al[16] reported previously that the effects of eczema and allergic sensitization interacted with the effect of *FLG* loss-of-function mutations on asthma but not rhinitis. "Preceding allergic sensitization and filaggrin variants" and "preceding eczema and filaggrin variants" increased the risk of subsequent asthma by 4.93- and 3.33-fold, respectively, in the first 18 years of life. Interaction was assessed on the multiplicative but not the additive scale. In our study we found that the presence of atopic dermatitis with allergic sensitization at age 1 year increased the risk of asthma more than 7-fold at age 3 years, with interacting effects on both the additive and multiplicative scales. Similar to the findings of Ziyab et al, we found no evidence to suggest an interactive effect on the risk of rhinitis. We were able to assess additional allergic outcomes, including atopic dermatitis and food allergy. Notably, atopic dermatitis and allergic sensitization at age 1 year had a

TABLE III. Interactive effects of atopic dermatitis and sensitization at age 1 year on subsequent allergic outcomes at age 3 years (n = 2311)

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Asthma at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	48/1825	Reference (1.0)	14/221	2.87 (1.60 to 5.14)†	2.87 (1.60 to 5.14)†
Atopic dermatitis	2/169	0.46 (0.11 to 1.93)	17/96	7.04 (4.13 to 11.99)†	12.46 (3.06 to 50.77)†
RR for atopic dermatitis within strata of sensitization		0.48 (0.11 to 2.00)		2.53 (1.31 to 4.91)†	
Interaction on multiplicative scale: aRR, 5.80; 95% CI, 1.20 to 27.83†					
Interaction on additive scale: RERI, 5.06; 95% CI, 1.33 to 11.04†					

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Allergic rhinitis at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	19/1825	Reference (1.0)	12/221	5.35 (2.70 to 10.60)†	5.35 (2.52 to 11.36)†
Atopic dermatitis	10/169	4.53 (2.13 to 9.63)†	13/96	11.75 (5.73 to 24.12)†	1.87 (0.78 to 4.49)
RR for atopic dermatitis within strata of sensitization		4.63 (2.08 to 10.31)†		2.35 (1.01 to 5.43)†	
Interaction on multiplicative scale: aRR, 0.49; 95% CI, 0.17 to 1.36					
Interaction on additive scale: RERI, 2.62; 95% CI, −5.48 to 14.05					

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Food allergy at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	21/1825	Reference (1.0)	36/221	13.76 (7.95 to 23.81)†	13.35 (7.68 to 23.21)†
Atopic dermatitis	5/169	2.50 (0.97 to 6.44)	41/96	33.79 (18.89 to 60.47)†	14.03 (5.71 to 34.45)†
RR for atopic dermatitis within strata of sensitization		2.14 (0.77 to 5.90)		2.18 (1.42 to 3.32)†	
Interaction on multiplicative scale: aRR, 0.77; 95% CI, 0.29 to 2.03					
Interaction on additive scale: RERI, 15.11; 95% CI, 4.19 to 35.36†					

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Atopic dermatitis at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	127/1825	Reference (1.0)	30/221	1.84 (1.27 to 2.68)†	1.84 (1.27 to 2.67)†
Atopic dermatitis	45/169	3.33 (2.44 to 4.55)†	48/96	6.00 (4.36 to 8.23)†	1.73 (1.24 to 2.39)†
RR for atopic dermatitis within strata of sensitization		3.28 (2.40 to 4.50)†		3.16 (2.08 to 4.79)†	
Interaction on multiplicative scale: aRR, 0.89; 95% CI, 0.54 to 1.45					
Interaction on additive scale: RERI, 1.44; 95% CI, −0.61 to 3.81					

*Adjusted for ethnicity, study center, pet ownership, parental atopy, child's sex, and parental history of any allergic diseases. Unadjusted values are available in Table E4 in this article's Online Repository at www.jacionline.org.
†Statistically significant at the .05 level.

highly significant positive interaction in the additive scale on the risk of food allergy.

The finding that sensitized children with atopic dermatitis at age 1 year had a significantly higher risk of food allergy at age 3 years is consistent with previous findings.[8,9] A potential explanation is that children shown to be sensitized to food allergens at age 1 year who also had atopic dermatitis might have consequently avoided the foods to which they were sensitized. We have previously shown in the CHILD study that children who avoided cow's milk products, egg, and peanut during the first year of life were at increased risk of allergic sensitization to the same foods.[30] A general pattern of delayed feeding was also associated with an increased risk of food sensitization. Because food sensitization is known to be on the pathway to food allergy, food avoidance might explain the substantial proportion of sensitized children with atopic dermatitis who have subsequent food allergy.

The potentially interactive effects of atopic dermatitis and allergic sensitization at age 1 year on allergic outcomes at age 3 years have not been well characterized. Previous studies have typically assessed atopic dermatitis and allergic sensitization as effect modifiers of the relationship between *FLG* variants and asthma or rhinitis[16] or assessed children with atopic dermatitis and allergic sensitization as a subgroup.[15]

A primary strength of our study was the longitudinal, population-based design. This allowed us to determine whether the finding of allergic sensitization in a 1-year-old child provides prognostic value alongside the presence of atopic dermatitis. We addressed this important research question by using objective skin prick test data at age 1 year and longitudinal clinic visit data up to age 3 years, with clear definitions of sensitization and atopic dermatitis. We found that atopic dermatitis and allergic sensitization could be combined to improve the prediction of all 4 of the allergic outcomes in our study. Moreover, we were able to report interaction on both the additive and multiplicative scales, which is a recommended practice in assessing the biological mechanism and public health effect of a disease.[27,28] Care must be taken in interpreting these results because of the wide CIs for some outcomes resulting from a low number of events at age 3 years.

We have not conducted genotyping for *FLG*, an epidermal protein that plays an important role in skin barrier function; subjects

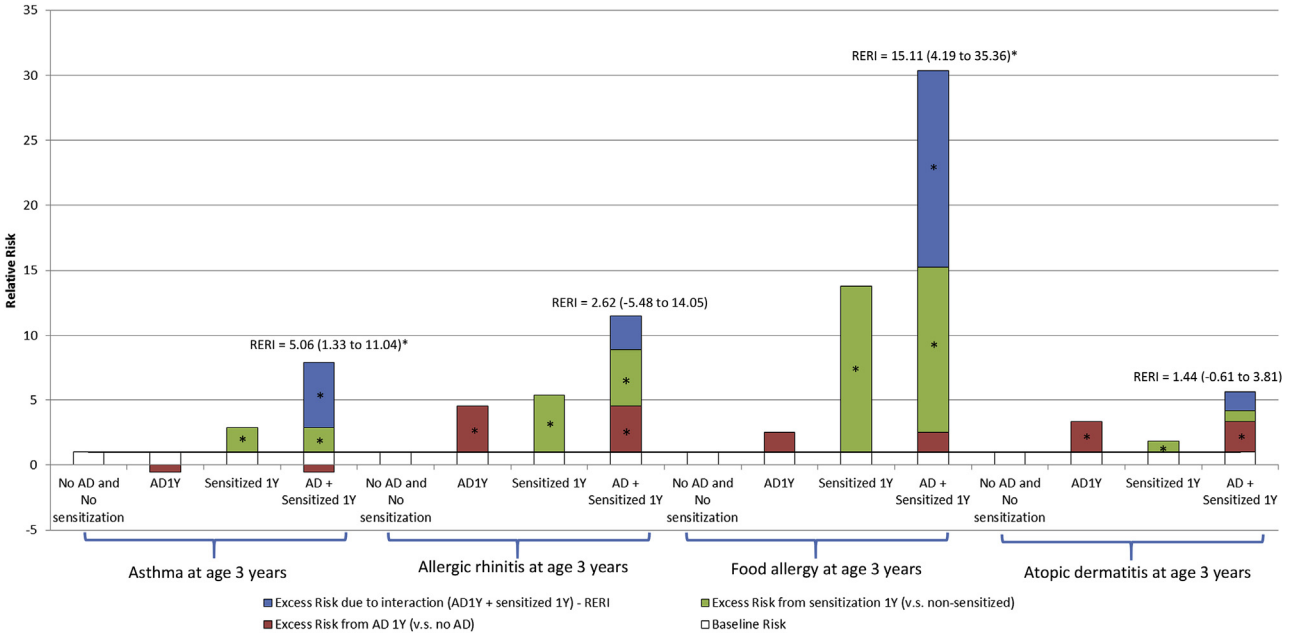

FIG 1. Interactive effects of atopic dermatitis *(AD)* and sensitization at age 1 year *(1Y)* on subsequent allergic outcomes at age 3 years (additive scale). *Significant at the .05 level. RERI and RR values are adjusted for child's sex, ethnicity, study center, pet ownership, parental atopy, and parental history of any allergic diseases. Unadjusted values are available in Fig E1 in this article's Online Repository at www.jacionline.org.

with *FLG*-deficient skin are predisposed to atopic dermatitis and have an increased risk of allergic rhinitis, food allergy, and asthma.[31-33] Although the majority of children with atopic dermatitis do not have an *FLG* loss-of-function mutation,[34] meta-analysis shows that *FLG*'s effect on atopic dermatitis risk is higher than that of any other confirmed candidate gene for atopic diseases.[35] Incorporating *FLG* mutations into our analyses alongside atopic dermatitis and allergic sensitization might have further strengthened the prediction of allergic outcomes in our study. However, *FLG* genotyping is a costly and invasive process that is not usually feasible in the clinical setting.

A potential limitation of our study was that cases of atopic dermatitis classified as definite by physicians or health care professionals during clinical assessments were likely more severe. Infants with milder atopic dermatitis might have been misclassified.[36] Future studies should investigate the relationship between low-to-moderate severity atopic dermatitis and allergic sensitization on the risk for allergic diseases. Additionally, food allergy was not confirmed by using oral challenges in our study, and we do not have a gold standard for the diagnosis of asthma at age 3 years. By using only definitive "yes" reports by experienced pediatric allergists and asthma specialists at the clinical visit at age 3 years rather than including reports of "possible," we have a conservative estimate of the prevalence of these diseases; the mix of steroid-treated (65%) and steroid-naive (35%) children given a diagnosis of definite asthma reflects the range of severity of illness in this group.

In conclusion, the atopic march refers to the natural progression of atopic dermatitis to asthma and allergic rhinitis. In a population-based, longitudinal birth cohort we compared allergic disease prognoses between sensitized and nonsensitized children with atopic dermatitis. We found that atopic dermatitis without allergic sensitization was not associated with increased asthma risk. Conversely, the combination of atopic dermatitis and allergic sensitization at age 1 year was associated with an increased risk of asthma and food allergy at age 3 years. The combined effect of atopic dermatitis and allergic sensitization was greater than the sum of their individual effects on the risk of food allergy and greater than the sum or the product of their individual effects on the risk of asthma. Children with atopic dermatitis and evidence of sensitization to common food or inhalant allergens as early as age 1 year represent a high-risk subgroup that warrants further examination in primary intervention studies.

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Clinical implications: The combination of atopic dermatitis with allergic sensitization at age 1 year predicts children who are more likely to have asthma and food allergy.

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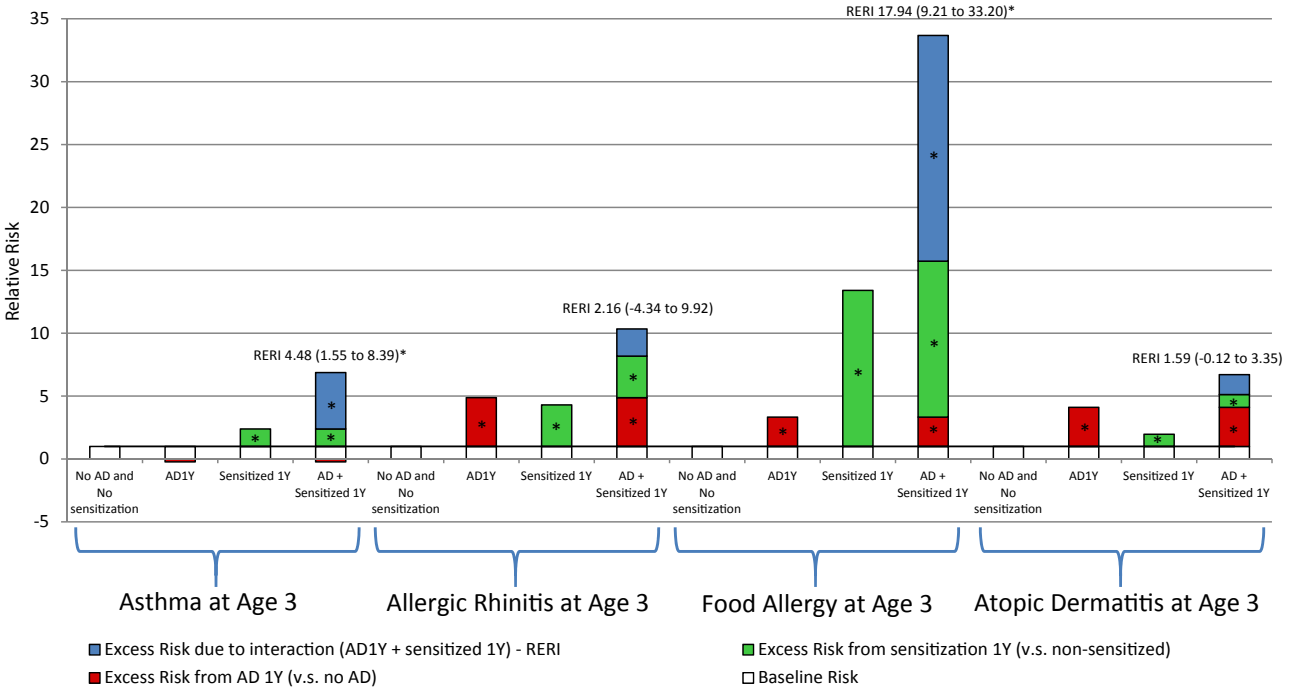

FIG E1. Interactive effects of atopic dermatitis *(AD)* and sensitization at age 1 year *(1Y)* on subsequent allergic outcomes at age 3 years (additive scale): unadjusted effects. *Significant at the .05 level.

TABLE E1. Comparisons of study sample with missing participants and full CHILD study cohort

Demographics	Study sample (n = 2311), no. (%)	Missing participants (n = 1166),* no. (%)	*P* value (sample vs missing)	Full cohort (n = 3495),* no. (%)	*P* value (sample vs full cohort)
Sex					
Male	1238 (53.6)	580 (50.6)		1818 (52.6)	
Female	1073 (46.4)	567 (49.4)	.10	1640 (47.4)	.46
Study center					
Edmonton	480 (20.8)	344 (29.5)		824 (23.7)	
Toronto	461 (20.0)	358 (30.7)		819 (23.5)	
Vancouver	558 (24.2)	230 (19.7)		788 (22.7)	
Winnipeg	812 (35.1)	234 (20.1)	<.001	1046 (30.1)	<.001
Skin test: mother					
≥1 Positive skin test response	1338 (58.3)	472 (55.1)		1343 (42.6)	
Negative responses on all skin tests	959 (41.8)	384 (44.9)	.12	1810 (57.4)	.53
Skin test: father					
≥1 Positive skin test response	1275 (68.0)	490 (69.3)		1765 (68.3)	
Negative responses on all skin tests	601 (32.0)	217 (30.7)	.51	818 (31.7)	.79
Parental atopy					
≥1 Positive skin test response	1855 (80.3)	731 (74.5)		2586 (78.6)	
Negative responses on all skin tests	456 (19.7)	250 (25.5)	.002	706 (21.5)	.12
Child's atopic status at age 1 y					
Any sensitization	317 (13.7)	97 (13.5)	.89	414 (13.7)	.96
Any food allergen	252 (10.9)	78 (10.9)	.98	330 (10.9)	.99
Peanut	118 (5.1)	26 (3.6)	.10	144 (4.8)	.56
Milk	43 (1.9)	11 (1.5)	.56	54 (1.8)	.83
Egg white	171 (7.4)	51 (7.1)	.79	222 (7.3)	.92
Any inhalant allergen	95 (4.1)	29 (4.0)	.93	124 (4.1)	.98
Nonsensitized	1994 (86.3)	621 (86.5)	.89	2615 (86.3)	.96
Atopic dermatitis at age 1 y					
Yes	265 (11.5)	96 (13.7)		361 (12.0)	
No	2046 (88.5)	607 (86.3)	.12	2653 (88.0)	.57
Mother's ethnicity					
First Nation	77 (3.3)	68 (6.1)		145 (4.2)	
Southeast Asian	298 (12.9)	121 (10.9)		420 (12.3)	
South Asian	50 (2.2)	66 (5.9)		116 (3.4)	
Black	41 (1.8)	32 (2.9)		73 (2.1)	
White	1742 (75.6)	757 (30.3)		2499 (73.1)	
Other	96 (4.2)	63 (39.6)		159 (4.7)	
Unknown	2 (0.09)	4 (0.06)	<.001	6 (0.2)	.03
Father's ethnicity					
First Nation	80 (3.5)	51 (4.6)		51 (4.6)	
Southeast Asian	243 (10.5)	87 (7.8)		87 (7.8)	
South Asian	73 (3.2)	61 (5.5)		61 (5.5)	
Black	62 (2.7)	45 (4.0)		45 (4.0)	
White	1755 (76.0)	777 (69.6)		777 (69.6)	
Other	86 (3.7)	85 (7.6)		85 (7.6)	
Unknown	11 (0.5)	11 (1.0)	<.001	11 (1.0)	.08
Atopic status at age 3 y					
Any sensitization	328 (14.6)	79 (13.7)	.61	407 (14.4)	.86
Any food allergen	133 (5.9)	27 (4.7)	.27	160 (5.7)	.71
Peanut	92 (4.1)	15 (2.7)	.10	107 (2.1)	.59
Milk	28 (1.3)	3 (0.5)	.14	31 (1.1)	.63
Egg white	55 (2.5)	8 (1.4)	.13	63 (2.2)	.62
Any inhalant allergen	215 (9.6)	47 (8.2)	.31	262 (9.3)	.73
Nonsensitized	1924 (85.4)	497 (86.3)	.61	2422 (85.6)	.86
Atopic dermatitis at age 3 y					
Yes	250 (10.8)	88 (15.4)		350 (12.2)	
No	2061 (89.2)	482 (84.6)	.007	2351 (87.9)	.14
Diagnosed asthma at age 3 y					
Yes	81 (3.5)	24 (4.2)		105 (3.6)	
No	2230 (96.5)	550 (95.8)	.44	2780 (96.4)	.80

(Continued)

TABLE E1. *(Continued)*

Demographics	Study sample (n = 2311), no. (%)	Missing participants (n = 1166),* no. (%)	*P* value (sample vs missing)	Full cohort (n = 3495),* no. (%)	*P* value (sample vs full cohort)
Allergic rhinitis at age 3 y					
Yes	54 (2.3)	15 (21.7)		69 (2.4)	
No	2257 (97.7)	559 (97.4)	.70	2816 (97.6)	.89
Food allergy at age 3 y					
Yes	103 (4.5)	21 (3.7)		124 (4.3)	
No	2208 (95.6)	553 (96.3)	.40	2761 (95.7)	.78
Household income					
$0-$49,999	310 (14.8)	81 (18.9)		391 (55.8)	
$50,000-$99,999	830 (40.0)	142 (33.1)		972 (38.7)	
$100,000-$149,999	554 (26.6)	116 (27.0)		670 (54.7)	
>$150,000	392 (18.8)	90 (21.0)	.03	482 (19.2)	.85
Parental history of allergic diseases					
Any allergic disease	2099 (90.8)	937 (85.5)	<.001	3040 (89.2)	.05
Atopic dermatitis	1746 (75.6)	750 (68.6)	<.001	2505 (73.6)	.09
Allergic rhinitis	1593 (68.9)	706 (64.5)	.006	2306 (67.7)	.34
Food allergy	768 (33.4)	302 (28.2)	.002	1075 (31.9)	.24
Asthma	818 (35.4)	335 (30.5)	.005	1154 (33.9)	.23
No parental history	212 (9.2)	159 (14.5)	<.001	367 (10.8)	.05

*Numbers might not add up to 1166 or 3495 because of missing data.

TABLE E2. Effects of atopic dermatitis and sensitization at age 1 year on subsequent allergic outcomes at age 3 years (n = 2311) by food versus inhalant sensitization

	Food sensitization at age 1 y (n = 252)			Inhalant sensitization at age 1 y (n = 95)		
Outcome at age 3 y	**No. of events (%)***	**Unadjusted RR (95% CI)**	**aRR (95% CI)†**	**No. of events (%)***	**Unadjusted RR (95% CI)**	**aRR (95% CI)†**
Asthma	28 (11.1)	4.32 (2.78-6.69)‡	4.58 (2.95-7.10)‡	7 (7.4)	2.21 (1.05-4.66)‡	2.64 (1.26-5.55)‡
Allergic rhinitis	19 (7.5)	4.44 (2.57-7.63)‡	3.54 (2.09-6.04)‡	8 (8.4)	4.06 (1.97-8.35)‡	4.74 (2.42-9.29)‡
Food allergy	76 (30.2)	23.00 (15.12-34.97)‡	20.38 (13.13-31.64)‡	9 (9.5)	2.23 (1.16-4.29)‡	1.77 (0.91-3.42)
Atopic dermatitis	69 (27.4)	3.11 (2.44-3.98)‡	2.63 (2.04-3.41)‡	18 (19.0)	1.81 (1.17-2.79)‡	1.53 (0.99-2.37)

*Percentage of events calculated among children who had food/inhalant sensitization at age 1 year.

†Adjusted for ethnicity, study center, child's sex, pet ownership, parental atopy, and parental history of any allergic diseases. Numbers for adjusted models are lower because of missing data required for adjustment.

‡Statistically significant at the .05 level.

TABLE E3. Interactive effects of atopic dermatitis and sensitization at age 1 year on subsequent allergic outcomes at age 3 years (n = 2311): Adjusted effects separated by food versus inhalant sensitization

	No food sensitization at 1 y		Food sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
Asthma at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	49/1878	Reference (1.0)	13/168	3.40 (1.88 to 6.14)†	3.41 (1.88 to 6.16)†
Atopic dermatitis	4/181	0.86 (0.31 to 2.40)	15/84	7.04 (4.08 to 12.17)†	6.21 (2.25 to 17.17)†
RR for atopic dermatitis within strata of sensitization		0.89 (0.32 to 2.48)		2.07 (1.04 to 4.11)†	
Interaction on multiplicative scale: RR, 2.60; 95% CI, 0.76 to 8.90					
Interaction on additive scale: RERI, 4.10; 95% CI, 0.11 to 9.87†					

	No food sensitization at 1 y		Food sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
Allergic rhinitis at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	23/1878	Reference (1.0)	8/168	3.60 (1.69 to 7.65)†	3.61 (1.70 to 7.66)†
Atopic dermatitis	12/181	4.46 (2.25 to 8.80)†	11/84	9.81 (5.04 to 19.10)†	1.68 (0.61 to 4.64)
RR for atopic dermatitis within strata of sensitization		4.56 (2.32 to 8.95)†		2.52 (0.85 to 7.52)	
Interaction on multiplicative scale: RR, 0.60; 95% CI, 0.20 to 1.77					
Interaction on additive scale: RERI, 1.98; 95% CI, −4.73 to 11.41					

	No food sensitization at 1 y		Food sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
Food allergy at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	21/1878	Reference (1.0)	36/168	18.42 (10.78 to 31.50)†	17.88 (10.42 to 30.69)†
Atopic dermatitis	6/181	2.74 (1.11 to 6.74)†	40/84	40.23 (22.37 to 72.34)†	14.27 (6.10 to 33.37)†
RR for atopic dermatitis within strata of sensitization		2.47 (0.94 to 6.51)		1.96 (1.30 to 2.95)†	
Interaction on multiplicative scale: RR, 0.60; 95% CI, 0.24 to 1.50					
Interaction on additive scale: RERI, 15.31; 95% CI, 1.98 to 38.84†					

	No food sensitization at 1 y		Food sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
Atopic dermatitis at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	132/1878	Reference (1.0)	25/168	1.99 (1.34 to 2.98)†	1.99 (1.34 to 2.98)†
Atopic dermatitis	49/181	3.31 (2.45 to 4.46)†	44/84	6.31 (4.54 to 8.77)†	1.80 (1.30 to 2.51)†
RR for atopic dermatitis within strata of sensitization		3.26 (2.41 to 4.41)†		3.09 (1.98 to 4.81)†	
Interaction on multiplicative scale: RR, 0.86; 95% CI, 0.51 to 1.43					
Interaction on additive scale: RERI, 1.56; 95% CI, −0.63 to 4.15					

	No inhalant sensitization at 1 y		Inhalant sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
Asthma at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	59/1975	Reference (1.0)	3/71	1.72 (0.54 to 5.43)	1.72 (0.54 to 5.42)
Atopic dermatitis	15/241	1.96 (1.12 to 3.41)†	4/24	6.30 (2.54 to 15.61)†	2.95 (1.06 to 8.24)†
RR for atopic dermatitis within strata of sensitization		2.00 (1.15 to 3.48)†		6.40 (0.79 to 51.56)	
Interaction on multiplicative scale: RR, 1.77; 95% CI, 0.41 to 7.70					
Interaction on additive scale: RERI, 3.49; 95% CI, −2.18 to 15.13					

	No inhalant sensitization at 1 y		Inhalant sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
Allergic rhinitis at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	27/1975	Reference (1.0)	4/71	5.40 (2.10 to 13.89)†	5.39 (2.09 to 13.87)†
Atopic dermatitis	19/241	4.30 (2.37 to 7.82)†	4/24	9.86 (3.59 to 27.07)†	3.84 (0.90 to 16.29)
RR for atopic dermatitis within strata of sensitization		4.36 (2.40 to 7.90)†		8.56 (0.55 to 134.02)	
Interaction on multiplicative scale: RR, 0.45; 95% CI, 0.12 to 1.61					
Interaction on additive scale: RERI, 2.02; 95% CI, −10.64 to 23.97					

	No inhalant sensitization at 1 y		Inhalant sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
Food allergy at age 3 y	**No. with outcome/total**	**RR (95% CI)***	**No. with outcome/total**	**RR (95% CI)***	
No atopic dermatitis	53/1975	Reference (1.0)	4/71	1.76 (0.64 to 4.85)	1.81 (0.65 to 4.98)
Atopic dermatitis	41/241	4.78 (3.12 to 7.33)†	5/24	4.29 (1.72 to 10.69)†	1.19 (0.53 to 2.67)

(Continued)

TABLE E3. *(Continued)*

Food allergy at age 3 y	No inhalant sensitization at 1 y		Inhalant sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
	No. with outcome/total	RR (95% CI)*	No. with outcome/total	RR (95% CI)*	
RR for atopic dermatitis within strata of sensitization		4.68 (3.03 to 7.25)†		4.07 (0.80 to 20.71)	
Interaction on multiplicative scale: RR, 0.54; 95% CI, 0.15 to 1.94					
Interaction on additive scale: RERI, −0.77; 95% CI, −5.76 to 6.86					

Atopic dermatitis at age 3 y	No inhalant sensitization at 1 y		Inhalant sensitization at 1 y		RR for sensitization within strata of atopic dermatitis
	No. with outcome/total	RR (95% CI)*	No. with outcome/total	RR (95% CI)*	
No atopic dermatitis	149/1975	Reference (1.0)	8/71	1.38 (0.70 to 2.72)	1.38 (0.70 to 2.72)
Atopic dermatitis	83/241	3.86 (3.00 to 4.95)†	10/24	3.92 (2.27 to 6.78)†	1.11 (0.67 to 1.83)
RR for atopic dermatitis within strata of sensitization		3.83 (2.98 to 4.92)†		7.42 (1.80 to 30.54)†	
Interaction on multiplicative scale: RR, 0.75; 95% CI, 0.32 to 1.74					
Interaction on additive scale: RERI, −0.20; 95% CI, −2.80 to 3.53					

*Adjusted for parental ethnicity, study center, pet ownership, parental atopy, child's sex, and parental history of any allergic diseases. Numbers are different from unadjusted models because of missing values.
†Statistically significant at the .05 level.

TABLE E4. Interactive effects of atopic dermatitis and sensitization at age 1 year on subsequent allergic outcomes at age 3 years (n = 2683): Unadjusted effects

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Asthma at age 3 y	**No. with outcome/total**	**RR (95% CI)**	**No. with outcome/total**	**RR (95% CI)**	
No atopic dermatitis	54/2116	Reference (1.0)	15/246	2.39 (1.37 to 4.17)*	2.39 (1.37 to 4.17)*
Atopic dermatitis	4/203	0.77 (0.28 to 2.11)	20/118	6.64 (4.12 to 10.72)*	8.72 (3.05 to 24.89)*
RR for atopic dermatitis within strata of sensitization		0.77 (0.28 to 2.10)		2.80 (1.49 to 5.28)*	
Interaction on multiplicative scale: RR, 3.65; 95% CI, 1.11 to 11.97*					
Interaction on additive scale: RERI, 4.48; 95% CI, 1.55 to 8.39*					

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Allergic rhinitis at age 3 y	**No. with outcome/total**	**RR (95% CI)**	**No. with outcome/total**	**RR (95% CI)**	
No atopic dermatitis	26/2116	Reference (1.0)	13/246	4.30 (2.24 to 8.26)*	4.30 (2.24 to 8.26)*
Atopic dermatitis	12/200	4.88 (2.50 to 9.53)*	15/118	10.35 (5.63 to 18.99)*	2.15 (1.04 to 4.43)*
RR for atopic dermatitis within strata of sensitization		4.86 (2.49 to 9.48)*		2.43 (1.19 to 4.93)*	
Interaction on multiplicative scale: RR, 0.50; 95% CI, 0.19 to 1.32					
Interaction on additive scale: RERI, 2.16; 95% CI, −4.34 to 9.92					

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Food allergy at age 3 y	**No. with outcome/total**	**RR (95% CI)**	**No. with outcome/total**	**RR (95% CI)**	
No atopic dermatitis	25/2113	Reference (1.0)	39/246	13.40 (8.25 to 21.75)*	14.32 (8.78 to 23.33)*
Atopic dermatitis	8/203	3.33 (1.52 to 7.29)*	47/118	33.66 (21.50 to 52.71)*	10.24 (5.01 to 20.93)*
RR for atopic dermatitis within strata of sensitization		3.45 (1.57 to 7.59)*		2.47 (1.72 to 3.54)*	
Interaction on multiplicative scale: RR, 0.75; 95% CI, 0.30 to 1.70					
Interaction on additive scale: RERI, 17.94; 95% CI, 9.21 to 33.20*					

	Nonsensitized at 1 y		Sensitized at 1 y		RR for sensitization within strata of atopic dermatitis
Atopic dermatitis at age 3 y	**No. with outcome/total**	**RR (95% CI)**	**No. with outcome/total**	**RR (95% CI)**	
No atopic dermatitis	149/2114	Reference (1.0)	34/245	1.97 (1.39 to 2.79)*	2.04 (1.45 to 2.88)*
Atopic dermatitis	58/200	4.11 (3.15 to 5.37)*	55/117	6.67 (5.21 to 8.54)*	1.64 (1.23 to 2.20)*
RR for atopic dermatitis within strata of sensitization		4.12 (3.16 to 5.38)*		3.32 (2.31 to 4.77)*	
Interaction on multiplicative scale: RR, 0.81; 95% CI, 0.51 to 1.26					
Interaction on additive scale: RERI, 1.59; 95% CI, −0.12 to 3.35					

*Statistically significant at the .05 level.

TABLE E5. Effects of atopic dermatitis and sensitization at age 1 year on subsequent allergic outcomes at age 3 years (n = 2311) comparing a 2-mm or greater wheal cutoff with a 3-mm or greater wheal cutoff to define sensitization

	Sensitization at age 1 y (≥2 mm wheals), n = 317			Sensitization at age 1 y (≥3 mm wheals), n = 214		
Outcome at age 3 y	**No. of events (%)***	**Unadjusted RR (95% CI)**	**aRR (95% CI)†**	**No. of events (%)***	**Unadjusted RR (95% CI)**	**aRR (95% CI)†**
Asthma	31 (9.78)	3.90 (2.53-6.01)‡	4.37 (2.85-6.69)‡	28 (13.08)	5.18 (3.35-8.00)‡	5.46 (3.53-8.44)‡
Allergic rhinitis	25 (7.89)	5.42 (3.22-9.14)‡	4.85 (2.84-8.27)‡	18 (8.41)	4.90 (2.83-8.48)‡	3.78 (2.12-6.74)‡
Food allergy	77 (24.29)	18.63 (12.14-28.59)‡	16.47 (10.64-25.49)‡	64 (29.91)	16.08 (11.08-23.34)‡	13.55 (8.97-20.47)‡
Atopic dermatitis	78 (24.61)	2.85 (2.24-3.63)‡	2.43 (1.89-3.12)‡	56 (26.17)	2.83 (2.18-3.68)‡	2.38 (1.81-3.13)‡

*Percentage of events calculated among children who had atopic dermatitis and allergic sensitization at age 1 year.
†Adjusted for ethnicity, study center, child's sex, pet ownership, parental atopy, and parental history of any allergic diseases. Numbers for adjusted models are lower because of missing data required for adjustment.
‡Statistically significant at the .05 level.