

The development and prediction of atopy in high-risk children: Follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance

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Background: The natural history of allergic disease and its potential for prevention merit close examination because of the explosive worldwide increase in the prevalence and morbidity of atopic disorders. This study examines the development of atopy at age 7 years in 165 children in a high-risk cohort, previously reported from birth to age 4 years.

Methods: In this prospective, randomized, controlled study of food allergen avoidance in infancy, the prophylactic-treated group consisted of infants whose mothers avoided cow's milk, egg, and peanut during the last trimester of pregnancy and lactation and who, themselves, avoided cow's milk until age 1 year (casein hydrolysate supplementation before age 1), egg until age 2 years, and peanut and fish until age 3 years. The control group consisted of maternal/infant pairs who followed standard feeding practices.

Results: Despite a significant reduction in food allergy and milk sensitization before age 2 years, none of the following differed between the groups at age 7 years: food allergy, atopic dermatitis, allergic rhinitis, asthma, any atopic disease, lung function, food or aeroallergen sensitization, serum IgE level, or presence of nasal eosinophils or nasal basophilic cells. Children with food allergy by 4 years evidenced higher 7-year (current) prevalences of allergic rhinitis and asthma ($p < 0.01$). Atopic diseases/parameters at age 7 years were shown, by multivariate analysis ($p < 0.05$), to be associated with several genetic and environmental risk factors (male gender, maternal nonwhite ethnicity and asthma, and household smoking), as well as predictive atopic markers during infancy (elevated serum IgE level; egg, cow's milk, and peanut sensitization; and nasal eosinophils and nasal basophilic cells).

Conclusions: These findings help to: (1) elucidate the natural history of atopic disease in high-risk children; (2) document the progression of allergy from atopic dermatitis, food allergy, and food sensitization to respiratory allergy and aeroallergen sensitization despite food allergy prevention in infancy; (3) identify allergy predictive markers; and (4) expand our appreciation of the interactions of genetic and environmental factors in the development of atopy. (*J ALLERGY CLIN IMMUNOL* 1995;95:1179-90.)

Key words: Food allergy, allergy prediction and prevention, atopy, asthma, allergic rhinitis, IgE, nasal eosinophils, nasal basophilic cells, environment, genetics, smoking, allergen sensitization

The formidable worldwide increase in both the prevalence and morbidity of atopic disease¹ lends particular urgency to the identification of strategies (interventions) to promote allergy prevention.

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Formulation of effective preventive strategies rests on building a more comprehensive framework for understanding the intricate interactions between the genetic and environmental factors responsible for the phenotypic expression of atopic disease. Most previous studies examining this interaction have relied either on retrospective examination of unselected subjects or, more recently, on a few prospective studies of high-risk children with only short-term follow-up.² These studies have implicated such genetic factors as atopic family history, male gender, parental ethnicity, sustained elevated total and specific IgE levels, defects in lymphocyte regulation, chromosomal mutations, and immune

Abbreviations used

CI:	Confidence interval
ETS:	Environmental tobacco smoke
FEF ₂₅₋₇₅ :	Forced expiratory flow between 25% and 75% of forced vital capacity
FEV ₁ :	Forced expiratory volume in 1 second
NBCs:	Nasal basophilic cells
NEs:	Nasal eosinophils
OR:	Odds ratio
SPT:	Skin prick test

response genes as integral to the development of atopy.²⁻¹⁰ Modulating environmental factors reported to be important in atopy expression have included early cow's milk formula feeding and solid food exposure, critical aeroallergen exposure during infancy, environmental tobacco smoke (ETS), spring or fall births, specific and early infections with viruses, and exposure to products of pollution.^{2, 9, 10-17}

In previous reports we noted that in a randomized, prospective, controlled study of offspring of atopic parents a comprehensive food allergen avoidance regimen, practiced by maternal/infant pairs during the perinatal period, reduced food sensitization and food allergy primarily during the first year of life, with a diminution of the benefit by 2 years and an absence of any benefit at ages 3 and 4 years.^{9, 18} Moreover, food allergen avoidance during infancy had no effect on respiratory allergy or aeroallergen sensitization from birth to age 4 years.⁹ This report evaluates the effect of this dietary prevention and the interaction of genetic, environmental, and atopic factors or parameters early in infancy on the development and prediction of atopy in this high-risk cohort at age 7 years.

METHODS

Study design

The design of the study, its protocol, subject recruitment, dietary interventions, and definitions of atopic outcomes have been detailed in previous reports^{9, 18} and will only be summarized here. Families from the Kaiser Foundation Health Plan of San Diego with an immunologically documented atopic parent were randomized before the third trimester of pregnancy into a maternal/infant food allergen avoidance group (prophylactic-treated group) or a standard maternal and infant dietary group (control group) as described previously, and infants were followed up from birth to age 4 years in the first phase of the study. This study, phase 2, requested these families to agree to a further follow-up evaluation at 7 years. A separate informed consent document for

the 7-year follow-up, approved by the Kaiser Foundation Hospitals Institutional Review Board, was read and signed by all families participating in this extended portion of the study.

Interventions

Prophylactic-treated group diet. Mothers were instructed with nutritionist supervision to avoid all cow's milk, egg, and peanut products and to supplement their diets with prenatal vitamins and calcium (to a total of 1500 mg daily) during the last trimester of pregnancy and the entire lactation period. Infants were breastfed or received a casein hydrolysate formula (Nutramigen; Mead Johnson Nutritional Division, Evansville, Ind.) as a substitute or supplement until 12 months of age. Solid foods were introduced in the following delayed manner: (1) nonlegume vegetables, rice cereal, meats, and non-citrus fruits between 6 and 12 months; (2) cow's milk, wheat, soy, corn, and citrus fruits between 12 and 18 months; (3) eggs at 24 months; and (4) peanut and fish at 36 months.

Control group diet. Mothers during pregnancy and lactation and infants after birth followed current standard dietary regimens recommended by the American Academies of Obstetrics and Gynecology and Pediatrics. Breastfeeding was encouraged and was substituted or supplemented with a cow's milk-based whey infant formula (Enfamil; Mead Johnson Nutritional Services) at the mother's discretion.

Interventions common to both groups. Breastfeeding was recommended for at least 4 to 6 months. Infant vitamin supplementation was left to the discretion of the personal pediatrician. Parents were encouraged, through information exchange (lecture, slide presentation, and brochures), to reduce household aeroallergens and to discontinue smoking.

Definitions of atopic disorders

The following criteria, as summarized below and detailed previously,¹⁸ were used to define the presence of atopic disorders from birth to 7 years.

1. Atopic dermatitis: An eczematous eruption associated with at least three of the following four criteria: (1) pruritis, (2) typical appearance and distribution, (3) a tendency toward chronicity or recurrence, and (4) concurrent specific IgE.
2. Urticaria/angioedema: A pruritic eruption or swelling with typical appearance observed by physician or parent, irrespective of cause.
3. Allergic rhinitis: A nasal condition with characteristic symptoms of sneezing, itching, and/or rhinorrhea with concurrent specific IgE and nasal eosinophils (NEs).
4. Asthma: Physician-documented lower respiratory disorder with reversible bronchospasm, occurring at least twice and unassociated with other anatomic, congenital, or immunologic causes.
5. Food allergy: Atopic dermatitis, urticaria/angioedema, or diarrhea/vomiting occurring on at least two

occasions or anaphylaxis induced by a specific food with concurrent food-specific IgE

Although double-blind, placebo-controlled food challenges were planned to confirm all adverse nonanaphylactic food reactions, only half of the parents consented to the procedure. Of those tested, 80% diagnosed with food allergy had positive results.¹⁸

Determination of immunologic outcomes

Skin prick tests (SPTs) were performed by Multitest (Lincoln Diagnostics Inc., Decatur, Ill.) puncture and intradermal techniques as described previously.¹⁸ Food allergens included 1:20 concentrations of cow's milk and egg and 1:10 concentrations of peanut, cod, shrimp, and walnut. Aeroallergens used included 1:50 concentrations of cat, dog, and mite; 1:20 concentrations of olive tree, grass mix (30% Bermuda, 70% grass mix); weed mix (equal parts ragweed, cocklebur, sagebrush, and sorrel); cockroach; and 1:10 concentrations of *Alternaria/Cladosporium* species (equal parts), *Helminthosporium/Aspergillus/Penicillium* species (equal parts) (Hollister-Stier, Division of Cutter Laboratories, Spokane, Wash.). Histamine phosphate (10 mg/ml for SPT and 0.1 mg/ml for intradermal testing), (Center Labs Inc., Port Washington, N.Y.) served as the positive control.

Total serum IgE levels were determined by Phadebas PRIST (Pharmacia, Uppsala, Sweden) as described previously.¹⁸

NEs and nasal basophilic cells (NBCs) were determined on nasal mucosal scrapings of the inferior turbinate by methods detailed previously.¹⁸

Urine cotinine levels, which were determined at American Health Foundation, Valhalla, N.Y., were quantitated by radioimmunoassay with interassay and intrassay variations of 5%, a sensitivity of 370 pg/ml for cotinine, and standardization to creatinine excretion and expression as cotinine to creatinine ratios.¹⁹

Spirometry was performed on a Collins S/560 spirometer (Warren E. Collins Inc., Braintree, Mass.) attached to an IBM PC (IBM, Danbury, Conn.) with option No. 1 of 560 software version 4.2 for predicted equations of lung functions based on age, height, sex, and corrected for African Americans.

Data analysis

Clinical and immunologic outcomes at 7 years were determined similarly to those determined at earlier ages.¹⁸ Prevalence definitions are those used previously: period prevalence is the proportion of subjects currently exhibiting a measured parameter, whereas cumulative prevalence is the proportion of subjects demonstrating the measured parameter at any past or current time. Significance was two-tailed and set at $p < 0.05$. Data were analyzed on an IBM mainframe computer or personal computer at the Biostatistical Division of the University of California-Los Angeles Health Services with the BMDP statistical software package version 1990 (BMDP Statistical Software, Inc., Los Angeles, Calif.).

Fisher's exact test or Pearson's chi square test was used for categorical univariate analyses. Student's t test and the Mann-Whitney U test evaluated continuous parametric and nonparametric data, respectively. Matched paired t tests or McNemar's chi square test compared data over time. Spearman's rank analysis was used for nonparametric correlations. Corrections were applied to multiple comparisons.

Data from study groups were combined when group differences did not exist for determination of atopic prediction and associations. For the basis of prediction, the following indices were calculated: sensitivity (probability of a positive test result in an affected individual), specificity (probability of a negative test result in a well individual), positive predictive value (probability that an individual with a positive test result is affected), negative predictive value (probability that an individual with a negative test result is not affected), efficiency (probability of correct classification), and rate ratio (risk of being affected with positive test result in relation to risk of being affected with negative test result). Multivariate logistic regression determined the odds ratio (OR) and 95% confidence intervals (CIs) of covariates that independently associated ($p < 0.05$) with the prevalences of atopic disorders and parameters. Stepwise linear regression determined the extent that various factors contributed to the variance of several atopic and environmental parameters at age 7 years.

RESULTS

Comparisons between prophylactic-treated and control groups

Subject retention. Of the prophylactic-treated ($n = 103$) and control ($n = 185$) subjects evaluated at 4 months, 59 (57%) and 106 (57%), respectively, agreed to or were available to participate in the follow-up at age 7 years. The similar rate of attrition in both groups derived from moves from San Diego or inability to locate ($n = 93$) and refusal to participate ($n = 30$). There was no apparent selective loss of subjects from ages 4 to 7 years. Those seen at 4 years but not at 7 years ($n = 65$) when compared with subjects seen at both times ($n = 160$) exhibited similar 4-year prevalences of allergic rhinitis, asthma, atopic dermatitis, food allergy, and food and aeroallergen sensitization. Comparability of study groups was seen in 18 demographic variables including parental ethnicity, schooling, occupation, smoking patterns, and home environmental characteristics (data not shown).

Growth patterns. Mean heights and weights at 7 years were similar in prophylactic-treated and control groups (124.9 ± 7.9 cm vs 124.6 ± 7.2 cm and 24.0 ± 3.6 kg vs 24.8 ± 4.7 kg, respectively).

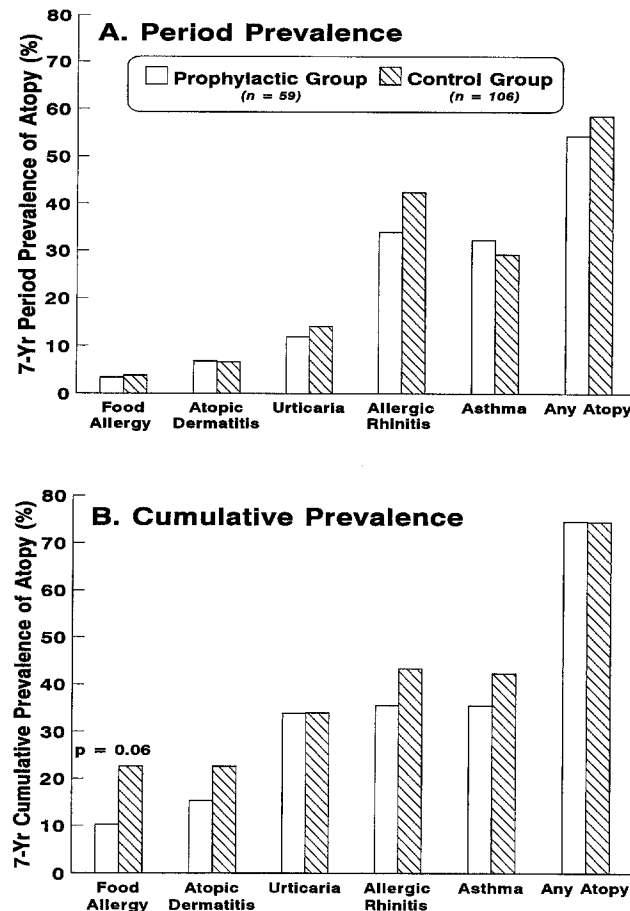


FIG. 1. The 7-year period (A) and cumulative (B) prevalences of atopic disorders in prophylactic-treated and control groups.

Nonfood allergy. Both the period (Fig. 1, A) and cumulative (Fig. 1, B) prevalences of atopic dermatitis, urticaria, allergic rhinitis, asthma, and any allergic disorder were similar in the two study groups at 7 years, even though the prophylactic-treated group demonstrated both lower period prevalences of atopic dermatitis and period and cumulative prevalences of at least one atopic disorder at age 1 year.¹⁸

Food allergy. Despite a lower period prevalence of food allergy at age 1 year in the prophylactic-treated group compared with the control group,¹⁸ at 7 years food allergy occurred to a similar extent in both groups (Fig. 1, A), as was also seen at 3 and 4 years.⁹ The cumulative prevalence of food allergy remained lower in the prophylactic-treated group compared with the control group at 7 years (Fig. 1, B) because of differences that occurred before 2 years.

Food SPT results, aeroallergen sensitization and serum IgE level. The period prevalence at 7 years

of children in the prophylactic-treated group compared with those in the control group, respectively, developing any positive food SPT result (13.9% vs 15.4%) or aeroallergen skin test result (39% vs 52.8%) was similar. Geometric mean serum IgE levels at 7 years were similar in the prophylactic-treated and control groups (32.4 ± 5.6 IU/ml and 42.9 ± 4.3 IU/ml, respectively).

Factors affecting atopy development in combined high-risk study cohort

Groups were combined when evaluating the development and prediction of atopy in this high-risk cohort when relevant data from both groups were similar.

Trends in atopy from 4 to 7 years. The period prevalences of allergic rhinitis (OR = 1.9, CI = 1.2-3.2) and of asthma (OR = 2.0, CI = 1.1-3.5) increased from 4 to 7 years in those children evaluated at both ages ($n = 160$) (Fig. 2, A).

Trends in aeroallergen and food sensitization from

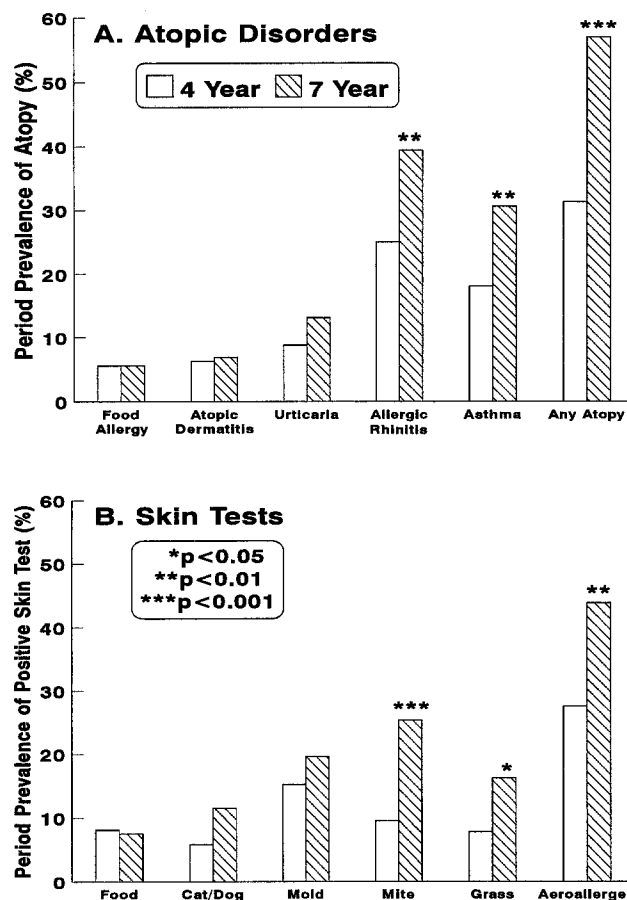


FIG. 2. Comparison of the 4-year and 7-year period prevalences of atopic disorders (A) and positive skin test results (B) in children from combined study groups evaluated at both periods ($n = 160$) (food = cow's milk, egg, peanut, or codfish; and mold = *Alternaria* or *Cladosporium* species).

4 to 7 years. Significant increases in the period prevalence of mite (OR = 3.2, CI = 1.6-6.5) and grass (OR = 2.3, CI = 1.1-5.1) sensitization occurred from 4 to 7 years, whereas sensitization to foods (cow's milk, egg, peanut, or cod fish) remained unchanged (Fig. 2, B). Foods associated with positive food SPT results at age 7 included in decreasing order of frequency: peanut ($n = 11$), walnut ($n = 9$), others ($n = 6$), shrimp ($n = 4$), egg and cod ($n = 2$), and milk ($n = 1$).

Trends and relationship of serum IgE levels to atopic parameters. Geometric mean serum IgE levels increased from 4 to 7 years (16.6 ± 5.6 IU/ml to 39.8 ± 4.8 IU/ml, $p < 0.001$). Serum IgE levels at age 7 showed: (1) strong correlations ($p < 0.01$) with serum IgE levels at 3 years (0.6890) and 4 years (0.7488); (2) moderate correlations ($p < 0.01$) with serum IgE level at 4 months (0.4837), 1 year (0.5043), and 2 years (0.5868) and with the number of atopic disorders (0.5095) and sum of aeroallergen skin tests (0.5377) at 7 years; and (3)

weak correlations ($p < 0.01$) with sum of food SPT results (0.3570), grade of NEs (0.4528), and grade of NBCs (0.3969) at age 7. In addition, geometric mean IgE levels at age 7 were significantly higher by three- to fivefold ($p < 0.01$) in children who had the following atopic conditions compared with those who did not: (1) any one of the atopic disorders, particularly atopic dermatitis; (2) allergen sensitization, especially to food; and (3) presence of NEs or NBCs.

Relationship of food allergy to development of allergic rhinitis and asthma. At age 7 the period prevalences of allergic rhinitis and asthma were almost two times greater in those children who had food allergy ($n = 31$) compared with those who did not have food allergy ($n = 134$) by 4 years (allergic rhinitis: 64.5% vs 33.6%, $p = 0.001$; asthma: 48.4% vs 26.1%, $p < 0.05$; and allergic rhinitis or asthma: 77.4% vs 45.5%, $p < 0.001$).

Factors related to the number of atopic disorders. The number of atopic disorders at age 7 correlated

TABLE I. Diagnostic capacity of NEs and NBCs for food and aeroallergenic sensitization at age 7 years in high-risk children in combined groups

Presence of nasal inflammatory cells at age 7	Diagnostic indices in percent	Diagnostic indices (%) for + skin test results at age 7		
		Any + food SPT	Any + aeroallergen skin test	Any + skin test
Eosinophils	Sensitivity	88	85	82
	Specificity	97	92	93
	Positive predictive value	30	90	91
	Negative predictive value	64	88	84
	Efficiency	68	89	87
	Rate ratio	0.8	7.2	5.8
	Significance (<i>p</i>)	<10 ⁻⁴	<10 ⁻⁴	<10 ⁻⁴
Basophilic cells	Sensitivity	79	76	73
	Specificity	94	81	82
	Positive predictive value	27	78	79
	Negative predictive value	61	79	76
	Efficiency	64	79	77
	Rate ratio	0.7	3.7	3.3
	Significance (<i>p</i>)	<10 ⁻³	<10 ⁻⁴	<10 ⁻⁴

Numbers of subjects with each atopic parameter used for above calculations: total subjects evaluated (*n* = 157-159), any positive (+) food SPT (*n* = 24), any + aeroallergen skin test (*n* = 74), and any + (aeroallergen or food) skin test result (*n* = 78).

directly (*p* < 0.01) with 7-year IgE level (noted above), number of positive food (0.4221) and aeroallergen (0.6901) skin test results, and grade of NEs (0.6807) and NBCs (0.5943). The total number of atopic disorders present at 7 years was greater in children who had compared with children who did not have positive food SPT results (2.3 ± 1.5 vs 0.7 ± 1.2), positive aeroallergen skin test results (1.6 ± 0.9 vs 0.3 ± 0.9), NEs (1.7 ± 0.8 vs 0.3 ± 0.9), and NBCs (1.5 ± 0.8 vs 0.4 ± 0.9) (*p* < 0.001 for all comparisons).

Relationship of NEs and NBCs to atopy. NEs and NBCs were present, respectively, in 44.0% and 45.3% of the children at 7 years, unchanged from age 4. The grade of NEs correlated strongly with NBC grade (0.8372, *p* < 0.001), and NE and NBC grades correlated (*p* < 0.01) with 7-year serum IgE level (noted above). Geometric mean serum IgE levels at 7 years were significantly higher in children with than without: (1) NEs (82.5 ± 3.9 IU/ml [*n* = 67] vs 21.5 ± 4.0 IU/ml [*n* = 83], *p* < 0.001) and (2) NBCs (70.2 ± 4.2 IU/ml [*n* = 69] vs 23.9 ± 4.2 IU/ml [*n* = 81], *p* < 0.001). NEs and NBCs were found significantly more frequently (*p* < 0.01) in children with atopic dermatitis, asthma, and positive food or aeroallergen skin test results and were highly diagnostic for food and aeroallergen sensitization (Table I).

Gender relationships. Boys, compared to girls, at age 7 years revealed significantly increased prevalences of various atopic conditions and parameters

(*p* < 0.05) including (1) serum IgE level (geometric mean, 48 ± 4.8 IU/ml vs 29 ± 4.1 IU/ml); (2) period prevalences of allergic rhinitis, asthma, any atopic disorder, aeroallergen skin tests, and NBCs; (3) cumulative prevalences of atopic dermatitis, asthma, and any atopic disorder; and (4) number of atopic disorders and grade of NEs and NBCs (data not shown).

Parental atopy relationships. Children whose mothers had asthma (*n* = 51) compared with children whose mothers did not (*n* = 114) experienced higher period (47.0% vs 22.8%, *p* < 0.01) and cumulative (52.9% vs 34.2%, *p* < 0.05) prevalences of asthma at 7 years.

Relationship of ETS to atopic parameters. Smoking occurred regularly in 13.3% of the 165 households. In validation of the self-reporting by parents, significantly higher (fourfold) levels of urinary cotinine were found in children residing in households in which ETS was reported (Table II); additionally, cotinine levels correlated with the total number of cigarettes smoked daily by parents (0.3718, *p* < 0.001). Household ETS exposure was associated with significantly reduced percent predicted forced expiratory volume in 1 second (FEV₁) and forced expiratory volume between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅), and higher prevalences and number of aeroallergen skin tests at 7 years (Table II). FEV₁ (% predicted) correlated inversely with urinary cotinine levels (-0.2219 , *p* < 0.05).

TABLE II. Relationship of ETS to atopic, spirometric, and smoke exposure parameters at age 7 years in high-risk children in combined groups

Parameter	Home ETS (n = 20-22 or as noted)	No home ETS (n = 141-143 or as noted)
Cotinine (ng/mg creatinine)	24.3 ± 20.7‡ (n = 15)	6.5 ± 6.4 (n = 115)
Serum IgE (IU/ml) (geometric)	52 ± 5.1	37 ± 4.7 (n = 136)
FEV ₁ (% predicted)	106 ± 14†	116 ± 16
FEV ₂₅₋₇₅ (% predicted)	90 ± 24*	103 ± 25
Asthma	36.4%	29.4%
Any atopic disorder	72.7%	54.5%
No. of atopic disorders/child	1.0 ± 0.9	0.9 ± 1.2
Positive food SPT results	14.3%	14.8%
Positive aeroallergen skin test results	68.2%*	41.9%
Positive aeroallergen skin test results/child	2.0 ± 2.1*	1.0 ± 1.6

Values are represented as percent of subjects or mean ± SD.

* $p < 0.05$.

† $p \leq 0.01$.

‡ $p < 0.001$.

Prediction of various atopic disorders and parameters

Atopic parameters present in infancy, which have been suggested to have relevance to atopy prediction later in childhood, include: (1) elevated serum IgE level; (2) food specific IgE, particularly egg; and (3) NEs and NBCs.² These predictive parameters were evaluated in this high-risk cohort at 7 years.

Cord blood IgE level. Cord blood IgE level greater than 0.5 IU/ml compared with 0.5 IU/ml or less exhibited for the current prevalences of atopy at 7 years: (1) high specificities and low sensitivities for atopic dermatitis, allergic rhinitis, allergen sensitization, and nasal inflammatory cells; (2) moderate predictive value for allergic rhinitis, any atopic disorder, positive aeroallergen skin test results, and nasal inflammatory cells; (3) high efficiency for atopic dermatitis; and (4) significant rate ratios for atopic dermatitis, allergic rhinitis, positive food and aeroallergen skin test results, and presence of NEs and NBCs (Table III).

Serum IgE level during infancy. An elevated serum IgE level, defined as 1 or more standard deviations above the geometric mean at 4 months, weakly predicted at 7 years only the period prevalence of atopic dermatitis (specificity = 45%, specificity = 86%, and rate ratio = 4.8; $p < 0.01$) and the cumulative prevalences of atopic dermatitis (sensitivity = 30%, specificity = 88%, and rate ratio = 2.2; $p < 0.05$) and any atopic disorder (sensitivity = 20%, specificity = 95%, and rate ratio = 1.3; $p < 0.05$). Serum IgE level of 1 or

more standard deviations at 1 year was not predictive for current allergy at 7 years ($p < 0.05$) but was weakly predictive for the cumulative prevalences of atopic dermatitis and any atopic disorder at age 7 ($p < 0.05$) (data not shown).

Positive egg SPT result by 1 year. The presence of a positive SPT response to egg by 1 year exhibited a high predictive capacity for atopic dermatitis and moderate predictive capacities for allergic rhinitis, asthma, and any atopic disorder at 7 years (Table IV).

Presence of NEs and NBCs by 1 year. NEs compared with NBCs by 1 year had better capacity to predict current atopic dermatitis, allergic rhinitis, and any atopic disorder at age 7 years (Table IV).

Atopic predictor factors evaluated by multivariate analyses. ORs and 95% CIs for various covariates, which exhibited significant predictive capacity ($p < 0.05$) for atopic disorders and parameters at 7 years are noted in Table V and include: (1) male gender, (2) maternal ethnicity, (3) parental asthma, (4) household ETS, (5) positive egg SPT result at ages 4 months and 1 year, (6) positive SPT responses to cow's milk and peanut at age 1 year, (7) presence of NEs and NBCs by age 1 year, and (8) food allergy by age 4 years. In separate logistic models, when added to the covariates used in Table V, elevated cord blood IgE level greater than 0.5 IU/ml remained predictive at age 7 years for aeroallergen sensitization (OR = 3.4, CI = 1.0-11; $p < 0.05$) and marginally for allergic rhinitis (OR = 2.8, CI = 0.9-9.4; $p < 0.09$).

Because the current prevalence of food allergy

TABLE III. Sensitivity, specificity, prediction, efficiency, and rate ratio indices of cord blood IgE level greater than 0.5 IU/ml with respect to the presence of atopic disorders, food and aeroallergen sensitization, and NEs and NBCs at age 7 years in high-risk children in combined groups

Prediction indices (%) of cord blood >0.5 IU/ml for various atopic parameters at 7 years									
Prediction indices	Atopic dermatitis	Urticaria	Allergic rhinitis	Asthma	Any atopic disorder	Positive food SPT result	Positive aeroallergen skin test result	NEs	NBCs
Sensitivity	40	15	22	11	17	25	19	20	20
Specificity	90	88	94	87	94	90	94	80	93
Positive predictive value	22	17	72	28	78	33	72	72	72
Negative predictive value	95	87	64	68	45	86	57	59	58
Efficiency	86	78	65	63	49	78	59	60	60
Ratio rate	4.7	1.3	2	0.9	1.4	2.3	1.7	1.7	1.7
Significance (p)	0.02	>0.1	0.003	>0.1	0.07	0.04	0.02	0.01	0.02

Total number of subjects evaluated ($n = 147$), cord blood IgE >0.5 IU/ml ($n = 18$); atopic dermatitis ($n = 10$); urticaria ($n = 20$); allergic rhinitis ($n = 59$); asthma ($n = 46$), positive food SPT result ($n = 24$); positive aeroallergen skin test results ($n = 68$); NEs ($n = 64$); NBCs ($n = 65$).

was especially low, only the cumulative prevalence of food allergy at age 7 could be satisfactorily evaluated by multivariate analysis. The following factors were shown by multivariate analysis to predict the development of food allergy by 7 years ($p < 0.05$): (1) control group (OR = 3.4, CI = 1.2-10), (2) male gender (OR = 3.0, CI = 1.1-7.9), (3) 4-month IgE ≥ 1 standard deviation (OR = 4.7, CI = 1.3-18), and (4) NEs by 1 year (OR = 6.2, CI = 1.5-25).

Atopic risk factors during infancy on the variability of serum IgE levels. Linear regression analysis with the same covariates noted in Table V revealed that log 4-month serum IgE contributed to 23% of the variance of the 7-year log serum IgE level ($p < 0.001$), with minor contribution from paternal atopic dermatitis (3.4%, $p < 0.05$) and positive SPT response to egg at 1 year (2.4%, $p < 0.05$).

Contribution of various factors to the variability of atopic parameters. Stepwise multiple linear regression reveals the contribution exerted by various risk factors concurrently present at 7 years to the variance in the level or extent of several atopic parameters occurring at age 7 (Table VI). From 6% to 36% of the variance of various atopic, spirometric, and environmental factors was exerted to varying degrees by multiple risk factors including male gender, maternal ethnicity, maternal and paternal IgE level, household and paternal

ETS, number of atopic disorders, 7-year serum IgE level, and sum of aeroallergen skin test results (Table VI).

DISCUSSION

This study represents the largest cohort of high-risk infants of atopic parents followed up for the longest duration in a randomized, controlled study evaluating the effect of combined maternal and infant food allergen avoidance on the development of allergic disease during childhood.

Development of atopic disease at age 7 years

The findings at 7 years document that perinatal maternal/infant food allergen avoidance compared with standard infant feeding practices: (1) failed to modify atopic disease at age 7 years, and, more specifically, after 2 years and (2) confirmed the findings at 3 and 4 years that the benefits of food allergy preventive efforts are of limited duration because of the frequent remission of food sensitization and food allergy in early childhood.

Studies have examined the effect of food allergen avoidance separately during gestation and lactation while controlling for the other routes of food allergen exposure.² Investigations from Sweden have convincingly documented that neither avoidance of nor ingestion of large quantities of

TABLE IV. Prediction indices (%) for positive SPT response to egg, NEs, or NBCs present by 12 months with respect to current atopy at age 7 years in high-risk children in combined groups

Presence of atopic factor $\leq$ 12 mo	Prediction indices	Prediction indices (%) for current atopic disease at age 7				
		Atopic dermatitis	Urticaria	Allergic rhinitis	Asthma	Any atopic disorder
Positive egg SPT response ($n = 25$)	Sensitivity	73	36	28	24	21
	Specificity	89	88	93	88	93
	Positive predictive value	32	32	72	48	80
	Negative predictive value	98	90	65	72	46
	Efficiency	88	81	67	68	51
	Rate ratio	15	3.2	2.1	1.7	1.5
	Significance (p)	<0.001	<0.01	<0.001	<0.05	<0.05
NEs ($n = 14$)	Sensitivity	40	19	21	14	14
	Specificity	93	93	99	94	98
	Positive predictive value	29	29	93	50	93
	Negative predictive value	96	88	66	71	46
	Efficiency	90	83	68	69	50
	Rate ratio	7.5	2.4	2.7	1.7	1.7
	Significance (p)	<0.001	<0.05	<0.001	0.1	<0.01
NBCs ($n = 71$)	Sensitivity	73	68	56	50	53
	Specificity	58	60	64	59	68
	Positive predictive value	11	20	51	35	69
	Negative predictive value	97	92	69	72	52
	Efficiency	59	59	61	56	59
	Rate ratio	3.7	2.5	1.6	1.3	1.4
	Significance (p)	<0.05	<0.05	0.01	>0.1	<0.01

Number of subjects with each atopic disorder used for above calculations: total subjects ($n = 160$ -162), atopic dermatitis ($n = 10$ -11), urticaria ($n = 21$ -22), allergic rhinitis ($n = 63$ -65), asthma ($n = 49$ -59), and any atopy ($n = 92$ -94).

cow's milk or egg during the third trimester of pregnancy affect the development of atopic disease or specific and total serum IgE from birth to 5 years.^{20, 21} Two studies^{22, 23} (only one of which was randomized²²), which examined the role of maternal food allergen avoidance during lactation, noted reductions in atopic dermatitis during infancy and before the age of 18 months, but with only minimal effects on specific IgE levels and no effect on respiratory disease. Such maternal lactation allergen avoidance diets implemented in the attempt to prevent atopy should be considered experimental until definitive studies are published.

The few investigations that have reported an allergy preventive effect of protein hydrolysates have done so only for atopic dermatitis and cow's milk allergy from infancy to the age of 18 months.^{22, 24-26} Consistent with the findings of this study, no effect was found on respiratory allergy prevention. Although these findings suggest an allergy preventive effect of protein hydrolysate feedings (particularly, the extensively hydrolyzed

hypoallergenic products) in high-risk infants when not breastfed or weaned, definitive studies are needed to determine whether extensive or partial hydrolysates are similarly effective in the prevention of cow's milk allergy and atopic dermatitis.²⁶

This and other studies^{9, 18, 22-26} have shown that food allergen avoidance during infancy without concurrent effective aeroallergen avoidance fails to affect atopic respiratory disease later in childhood. One recent study, which added anti-dust mite measures (acaricide treatments and impermeable bedding encasings) to combined maternal/infant food allergen avoidance in high-risk infants, reported reductions in both asthma and atopic dermatitis by the age of 1 year.²⁷ At age 2 years, the reduction in the current prevalence of asthma was not significant; though the reduction in combined food and aeroallergen sensitization was.²⁸ It is too early to know the long-term effects of such combined dietary and environmental allergy prevention measures; however, the likelihood that families will readily institute environmental avoidance

TABLE V. Risk factors for predicting atopy at age 7 years determined by multivariate regression in high-risk children in combined groups

Covariate predictor factors	ORs and (95% CIs) for 7-year period (current) prevalence of atopic parameter								
	Atopic dermatitis	Urticaria	Allergic rhinitis	Asthma	Any atopic disorder	Positive food SPT response	Positive aeroallergen skin test response	NEs	NBCs
Male gender			2.1* (1.0-4.4)	4.3‡ (1.8-9.9)	2.7† (1.3-5.5)		2.5† (1.3-5.2)		2.1* (1.1-25)
Maternal ethnicity (nonwhite)							2.9* (1.0-8.4)		
Maternal asthma				4.1‡ (1.9-9.2)		4.4* (1.4-14)			
Paternal asthma			3.1* (1.1-8.8)			5.1‡ (1.4-19)			
Paternal ETS	7.9* (1.0-61)								
Household ETS							2.9* (1.0-8.2)		
Egg SPT 4-month		11.1* (1.4-86)							
Milk SPT 1-year				6.0* (1.3-28)					
Peanut SPT 1-year	34* (1.5-794)			11.2* (1.2-107)					
NEs 1-year			1.8* (1.1-3.1)				1.8* (1.1-2.9)	1.7* (1.0-2.8)	
NBCs 1-year		4.2* (1.3-13)			2.7† (1.3-5.7)	1.4† (1.1-1.9)			
Food allergy ≤4-years	23† (3.0-176)		2.8* (2.6-7.1)		3.9* (1.2-12)		3.1* (1.2-8.1)	4.2† (1.5-12)	

Covariates not entering any of above models ($p > 0.09$) included: study group, paternal ethnicity, maternal or paternal atopic dermatitis, maternal smoking, 4-month serum IgE level, peanut and milk 4-month SPT, nasal eosinophils or basophilic cells at 4 months.

Total subjects ($n = 149-154$): presence of atopic dermatitis ($n = 9$), urticaria ($n = 20$), allergic rhinitis ($n = 63$), asthma ($n = 49$), any atopy ($n = 91$), positive food SPT response ($n = 22$), positive aeroallergen skin test ($n = 71$), NEs ($n = 68$), and NBCs ($n = 69$).

* $p \leq 0.05$.

† $p \leq 0.01$.

‡ $p \leq 0.001$.

measures over the long term may be suboptimal, even if they are given intensive environmental advice.²⁹

Prediction of atopic disease at age 7 years in high-risk children

Initial reports raised enthusiasm that elevated neonatal IgE level and diminished T-lymphocyte subsets could predict allergic disease.² Many recent studies have been unable to confirm the level

of prediction of these earlier findings.³⁰⁻³² Elevated cord blood IgE in this study demonstrated some predictive capacity, but after multivariate analysis, only significantly for aeroallergen sensitization. As such, neonatal IgE determination for allergy prediction cannot be recommended for the general population but may still have relevance in identifying high-risk neonates for allergy prevention studies.³⁰

Specific IgE to foods (egg, cow's milk) deter-

TABLE VI. Factors affecting the development of various atopic parameters at age 7 years determined by stepwise multiple linear regression analysis in high-risk children in combined groups

Covariate factor at 7 years	Variance in atopic/spirometric/environmental factor at age 7 years (R ² in %)*								
	Log IgE level	NE grade	NBC grade	FEV ₁ (% predicted)	FEF ₂₅₋₇₅ (% predicted)	Sum + food SPT	Sum + aeroallergen skin tests	Sum atopic disorders	Cotinine (ng/mg Cr)
Male subject				13.0%					
Maternal ethnicity (nonwhite)		2.3%				6.9%		5.8%	
Maternal log IgE							2.9%		
Paternal log IgE	2.3%								
Home ETS				3.1%	2.5%				3.6%
Paternal ETS									31.9%
Atopic dermatitis			2.2%						
Allergic rhinitis	25.4%	22.4%	16.7%						
Asthma	3.3%	4.1%	7.5%		3.9%				
Log IgE level						9.9%	24.3%	24.0%	
Multiple R²	31.0%	28.8%	26.4%	16.1%	6.3%	16.8%	27.3%	29.7%	35.5%

Covariates not entering any of above models ($p > 0.09$) included: study group, sum of maternal and paternal cigarettes daily, sum of food SPT results, sum of positive aeroallergen skin test results, maternal and paternal education level, and paternal occupation. +, Positive; Cr, creatinine.

*Significance; $p < 0.05$ for all R² values noted. (Multiple R² values may not add up exactly because of rounding off.)

mined by RAST (score ≥ 1) or SPT in infancy has been suggested to have allergy predictive capacity by age 18 months in a high-risk cohort³² and at ages 18 months and 7 years in an unselected cohort.³¹ In this high-risk cohort in which the prevalence of allergic disease was high ($>50\%$), atopic markers in infancy such as specific food IgE (egg, cow's milk, and peanut) and NEs, and NBCs exhibited high positive predictive value for many atopic disorders and for food and aeroallergen sensitization, confirming and extending earlier observations.^{31, 32} Determination of these atopic markers (factors) during infancy may provide an impetus for initiating allergy preventive efforts in high-risk infants. Rather simple and inexpensive screening tests, such as food SPTs (egg, cow's milk, and peanut) and nasal cytologic examinations for eosinophils obtained during infancy could help identify with greater certainty those high-risk infants who will become atopic in childhood. Such identification should increase the cost-effectiveness of implementing allergy preventive measures and provide a cohort of high-risk infants that could benefit from facilitated referral to allergists to direct the preventive strategy.

Genetic and environmental risk factors for atopy at age 7

Genetic factors such as male gender, parental asthma, ethnicity, and environmental factors such as household and parental smoking influenced both the presence (Table V) and extent (Table VI) of atopy at 7 years, as also noted by age 4 years in an earlier evaluation of this cohort⁹ and reviewed elsewhere.³³ Though not specifically determined by this study, other investigations have reported the importance of environmental factors such as the exposure to dust mite and other aeroallergens in infancy.¹³ Although genetic factors remain unmodifiable, environmental ones such as allergen and ETS exposure are potentially changeable and deserve modification in an attempt to halt the ravages of atopic disease. Future investigations should be able to determine whether such allergy preventive efforts will succeed in countering the alarming increase in the prevalence of atopic disease.

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