

The Canadian asthma primary prevention study: Outcomes at 2 years of age

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Background: Avoidance of individual risk factors have not been successful in preventing the development of asthma.

Objective: We sought to determine the effectiveness of a multifaceted intervention program in primary prevention of asthma in high-risk infants.

Methods: We identified 545 high-risk infants on the basis of an immediate family history of asthma. Families were randomized into intervention or control groups. Intervention measures included avoidance of house dust mite, pet allergen, and environmental tobacco smoke. Breast-feeding was encouraged with formula supplementation if necessary, and introduction of solid foods was delayed.

Results: At 2 years of age, 19.5% of the children had asthma, and 14.7% had atopy (positive skin test response to one or more common allergens). Significantly fewer children had asthma in the intervention group compared with in the control group (16.3% vs 23.0%), with 60% less persistent asthma at 2 years. There was a 90% reduction for recurrent wheeze in the intervention group compared with that seen in the control group. Exposure to maternal environmental tobacco smoke during pregnancy or the first year was a risk factor for asthma at 2 years of age. A positive skin test response, particularly to food, at 12 months predicted asthma at 2 years. There was no significant difference for atopy between the intervention and control groups, but daycare reduced atopy at 2 years.

Conclusion: This multifaceted intervention program during a window of opportunity in the first year of life was effective in preventing asthma in high-risk children at 2 years of age.

Future studies with this cohort at school age are important. (J Allergy Clin Immunol 2004;113:650-6.)

Key words: Asthma, atopy, risk factors, primary prevention, environmental tobacco smoke, daycare, breast-feeding, early life

Over the past quarter century, the prevalence of asthma has increased to epidemic proportions in the industrialized

Abbreviations used

ETS: Environmental tobacco smoke

HDM: House dust mite

OR: Odds ratio

world and is the most common chronic disease in children.^{1,2} Asthma and other atopic disorders are complex diseases with a strong heritable component and multiple environmental influences; that is, asthma is a disease that arises from gene-environment interactions. In addition to the overall familial concordance of atopy, development of allergic rhinitis, atopic dermatitis, or asthma appears to be specifically inherited.³ The rapidly increased asthma prevalence observed over the past few decades is unlikely related to genetic changes. Therefore we focused our approach to primary prevention of asthma on early-life environmental influences that might be modified in families with a strong history of asthma. Sensitization to aeroallergens,^{4,6} allergy to foods (particularly to egg⁷), and exposure to environmental tobacco smoke (ETS) early in life⁸⁻¹⁰ are major risk factors for asthma. On the basis of available data, we undertook a prospective, randomized, controlled study to determine the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants.

To our knowledge, there had only been one prospective, randomized, controlled study on the primary prevention of asthma in high-risk infants. In that study control of house dust mite (HDM) exposure and food avoidance was associated with a significant decrease in recurrent wheezing at 12 months but not by 2 or 4 years of age.¹¹⁻¹³ There have also been several studies addressing the effect of breast-feeding and food allergen avoidance on the development of allergy and asthma. A meta-analysis¹⁴ of these studies demonstrated a 20% decrease in the risk for asthma with breast-feeding (odds ratio [OR], 0.80; 95% CI, 0.66-0.97). In a more recent epidemiologic study, Oddy et al¹⁵ assessed the effect of exclusive breast-feeding in children 6 years of age and demonstrated that introduction of milk other than breast milk before 4 months of age was a risk factor for increased likelihood of asthma, with an OR of 1.25 (95% CI, 1.02-1.52).

We focused our multifaceted intervention on decreasing exposure to common indoor allergens, encouraging breast-feeding, delaying introduction of other foods, and avoiding ETS during the first 12 months of life in infants at high risk asthma. We hypothesized that intervention

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during this window of opportunity has the potential for long-term modification of the infant's risk for asthma. We previously reported that asthma was significantly reduced at 12 months of age by 34% in the intervention group compared with in the control group.¹⁶ We now report outcomes in this cohort of children at 2 years of age.

METHODS

Study population

Our Canadian Asthma Primary Prevention study is a prospective, prenatally randomized, controlled clinical trial in a cohort of children at high risk for development of asthma on the basis of an immediate family history. This cohort has been described in a previous communication.¹⁶ Briefly, high-risk infants, defined as those with at least one first-degree relative with asthma or 2 first-degree relatives with other classic IgE-mediated allergic diseases, had families identified during the mother's third trimester of pregnancy. Mothers were randomly allocated to our multifaceted intervention program (n = 278) or to the control group (n = 267). Infants born between October 1994 and August 1996 included 4 pairs of twins, 2 in each of the groups (total n = 549). At 12 months of age, we assessed 251 (89.6%) infants in the intervention group and 242 (90.0%) infants in the control group. At 2 years of age, 246 (87.9%) children were available for assessment in the intervention group, and 230 (85.5%) children were available in the control group. Dropouts were not significantly different between the 2 groups.

Study protocol

Home visits were carried out during the third trimester of pregnancy, at 2 weeks, and at 4, 8, 12, 18, and 24 months after the birth of the child. Demographic and health characteristics were gathered by using a standardized questionnaire, and home characteristics were assessed by using a questionnaire and a walk-through survey. After baseline assessment, a sealed envelope was opened that determined the family's allocation to the intervention or control group. The control group did not receive specific information about intervention measures but followed the usual care recommended by their primary care physicians.

Intervention

The multifaceted intervention program undertaken during the first year of life has been previously described.¹⁶ Briefly, HDM control included encasement of the infant's mattress plus all mattresses and box springs in the parent's bedroom. Families were instructed to wash all bedding weekly using the hot cycle of their washing machines. We applied benzyl benzoate powder to carpets in the infant's and parent's bedrooms and in the most commonly used room, and benzyl benzoate foam was applied to upholstered furniture in the most commonly used room before and at 4 and 8 months after birth. Families were counseled to remove cats, dogs, or both from the home. Where this was not possible, they were instructed to keep pets outside the home or at least outside the infant's bedroom. For ETS, parents were counseled on smoking cessation, and families were instructed to keep homes smoke free. Families were encouraged to avoid daycare until after the first year of life. At each visit, nurses reinforced various avoidance measures.

Mothers were encouraged to breast-feed for at least 4 months and for the first year if possible. Where breast-feeding was not possible, partially hydrolyzed whey formula (Good Start; Nestle Canada Inc, North York, Ontario, Canada) was supplied for supplementation until 12 months of age.

House dust sampling and determination of allergen levels. During each visit, dust samples were collected from 6 sites:

the infant's and parent's bedroom floor and mattress and the floor and upholstered furniture in the most commonly used room.¹⁷ Samples were analyzed in duplicate for HDM and cat allergen by using ELISA with purified mAbs against group 1 mite allergens, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Der p 1 and Der f 1), and cat allergen, Fel d 1.^{18,19} Total mite allergen (sum of Der p 1 and Der f 1) was reported as micrograms per gram of dust.¹⁶ Allergen from 5 sites (excluding the infant's mattress because levels were uniformly not detectable) at each time was averaged.

Outcome assessment at 2 years. Assessment at 2 years was carried out in the same way as for the 12-month assessment. Each child was seen by a pediatric asthma specialist blinded to study group and to compliance with intervention and who did not provide health care to the families. They examined the child and conducted a structured interview to record symptoms and physical findings. *Possible asthma* was defined as at least 2 distinct episodes of cough, each lasting for 2 or more weeks; at least 2 distinct episodes of wheeze, each lasting 2 or more weeks; or, in the absence of a cold, at least one of the following: nocturnal cough (at least once a week) and hyperpnea-induced cough or wheeze (eg, with crying, laughing, or activity). *Probable asthma* was defined as at least 2 distinct episodes of cough, each lasting 2 or more weeks, or at least 2 distinct episodes of wheeze, each lasting 1 or more weeks, and at least one of the following: nocturnal cough (at least once a week) in the absence of cold, hyperpnea-induced cough or wheeze, response to treatment with β -agonist, anti-inflammatory drugs, or both.

Recurrent wheeze was defined as 3 or more episodes of wheezing, each lasting 1 week or more, and *recurrent cough* was defined as 3 or more episodes, each lasting 2 or more weeks.

Rhinitis without colds was defined as 2 or more episodes of runny nose and sneezing in the absence of an apparent cold.

Allergy skin tests (epicutaneous) used a prick Lanceter (Bayer Inc) with the following allergens (Bayer Inc): HDM (*D pteronyssinus* and *D farinae*), cat, dog, cockroach, *Alternaria* species, *Cladosporium* species, cow's milk, egg white, wheat, soy, and peanut. Histamine (1 mg/mL) was the positive control, and saline was the negative control. The largest wheal diameter and its perpendicular were measured 15 minutes after testing. A mean wheal diameter 3 mm or greater than that elicited by the negative control was considered positive. Atopy was defined as a positive skin test response to one or more allergen.

Ethics

The Ethics Committees of the University of British Columbia and the University of Manitoba approved the study.

Statistical analysis

There were no differences between characteristics of the families and children in the control and intervention groups, except for higher prevalence of mothers in the control group receiving postsecondary education.

Because the infants were in 2 groups and assessed twice, there were 2 $\times$ 2 response profiles: no-no, no-yes, yes-no, and yes-yes. No-no was the profile with absence of outcome (eg, asthma) in both years, and yes-yes was the profile with outcome in both years. Asthma was analyzed as the sum of children with a diagnosis of both possible and probable asthma. Distribution of outcome profiles was compared between the control and intervention groups, and ORs with 95% CIs were estimated and adjusted for maternal education and child's sex. The CATMOD procedure for modeling repeated-measurements data with a dichotomous outcome was used. This method allows adjustment for between-subject variation and within-subject variation resulting from 2 time points, year 1 and year 2, measured for each subject. The analysis assessed both types of variation in addition to their interaction. Analyses were conducted that randomly excluded one

TABLE I. Prevalence of asthma and atopy at year 1 and 2

Year	Control group, n (%)	Intervention group, n (%)	OR (95% CI), unadjusted	OR (95% CI), adjusted*
Asthma†				
Year 1	46 (20.0)	38 (15.5)	0.73 (0.46-1.18)	0.68 (0.42-1.09)
Year 2	53 (23.0)	40 (16.3)	0.65 (0.41-1.03)	0.60 (0.37-0.95)
Year 1 and 2	26 (11.3)	12 (4.9)	0.40 (0.20-0.82)	0.36 (0.17-0.73)
Atopy‡				
Year 1	49 (21.7)	52 (21.2)	0.98 (0.63-1.52)	0.96 (0.61-1.50)
Year 2	31 (13.7)	38 (15.6)	1.16 (0.69-1.94)	1.13 (0.68-1.91)
Year 1 and 2	23 (10.2)	29 (11.9)	1.19 (0.67-2.13)	1.20 (0.67-2.15)

*Adjusted for differences in maternal education and sex of the child.

†Asthma is defined as noted in the Methods section as the sum of possible and probable asthma. Possible asthma was described as 2 distinct episodes of cough, each lasting for 2 or more weeks; at least 2 distinct episodes of wheeze, each lasting 1 or more weeks; or, in the absence of a cold, at least one of the following: nocturnal cough, hyperpnea-induced cough, or wheeze. Probable asthma was defined as at least 2 distinct episodes of cough or 2 episodes of wheeze and at least one of the following: nocturnal cough at least once a week (in the absence of a cold), hyperpnea-induced cough or wheeze, response to treatment with β -agonists, anti-inflammatory drugs, or both.

‡Atopy was defined as a positive skin test reaction to one or more common inhalant or ingestant allergens.

child from each of the 4 pairs of twins. This did not affect the results, and the current model includes all children.

Univariate analyses with χ^2 tests initially explored the association of confounders with asthma and atopy at 2 years. Potential confounders were as follows: ethnicity, sex, mother's history of atopy, mother's education, and center effect. These potential confounders comprised the basic model.

Statistical analysis was carried out with SPSS/PC Version 9 (SPSS) and Stata statistical software, version 6.0 for Windows 8 (Stata Corp).

RESULTS

Efficacy of interventions

We previously reported the success of our multifaceted intervention program.^{16,20} In summary, we successfully decreased HDM exposure in the first and second year (first-year average Der p 1 plus Der f 1: intervention vs control, 1.69 vs 2.70 $\mu\text{g/g}$; second year: 1.28 vs 2.45 $\mu\text{g/g}$). Although prevalence of pets did not change, there was significantly less cat allergen exposure at 2 weeks and 4 months in intervention homes (first-year average Fel d 1, 1.68 vs 2.09 $\mu\text{g/g}$; second year, 2.24 vs 2.5 $\mu\text{g/g}$). Mothers in the intervention group breast-fed longer and delayed introduction of solid food. Significantly fewer children in the intervention group were in daycare by 1 year. Finally, there was less ETS exposure, with fewer visitors smoking in intervention homes.

Prevalence of asthma and atopy at 2 years

At 2 years, 93 (19.5%) children in this high-risk cohort satisfied the criteria of having asthma, and 69 (14.5%) had positive skin test responses to at least one common allergen. At 2 years, 40 (16.3%) of 246 children in the intervention group and 53 (23.0%) of 230 control children had asthma, and 38 (15.6%) of 246 children in the intervention group and 31 (13.7%) of 230 control children were atopic.

Table I shows the prevalence of asthma and atopy, comparing the control and intervention groups adjusted for differences in maternal education and sex of the children. Some children had asthma during the first year of

life (year 1) but not during the second year. Other children had asthma during the second year of life (year 2). Some children had asthma in year 1 that was persistent into the second year of life (year 1 and 2). Conversely, 177 (72.0%) of 246 children in the intervention group never had an asthma diagnosis compared with 156 (67.8%) of 230 control children.

Our multifaceted intervention had a significant effect on the prevalence of asthma at age 2 years, decreasing the number of children given a diagnosis of possible and probable asthma in the intervention group (16.3%) compared with in the control group (23.0%; OR, 0.60; 95% CI, 0.37-0.95). Asthma was more likely to occur in the control group than in the intervention group and was as likely to occur in the first year as in the second year. The main difference between the control and intervention groups was in the substantial reduction of persistent asthma (ie, asthma present at both year 1 and 2) in the intervention group (4.9% vs 11.3%; OR, 0.36; 95% CI, 0.17-0.73; Table I and Fig 1). New asthma in the second year among those free of asthma in the first year was similar in the control and intervention groups.

Although we applied a rigorous definition to the diagnosis of asthma, we also analyzed data for recurrent wheeze and recurrent cough. In the first year, recurrent wheeze was not different between the control and intervention groups. Recurrent cough at year 1 had an OR of 0.53 (95% CI, 0.27-1.04) but did not reach significance (Fig 2, A). Recurrent cough at year 2 did not discriminate between the groups (OR, 0.68; 95% CI, 0.36-1.29). However, at 2 years of age, significantly fewer children had recurrent wheeze in the intervention group compared with in the control group (OR, 0.10; 95% CI, 0.01-0.84; Fig 2, B).

The prevalence of atopy at year 2 was not different between the control (13.7%) and intervention (15.6%) groups. However, there was a significant decrease in atopy in the entire cohort from year 1 to year 2 (Table I), mainly related to loss of sensitivity to cow's milk and egg.

Significantly more children with asthma had a positive skin test response to any allergen (6.5%) compared with

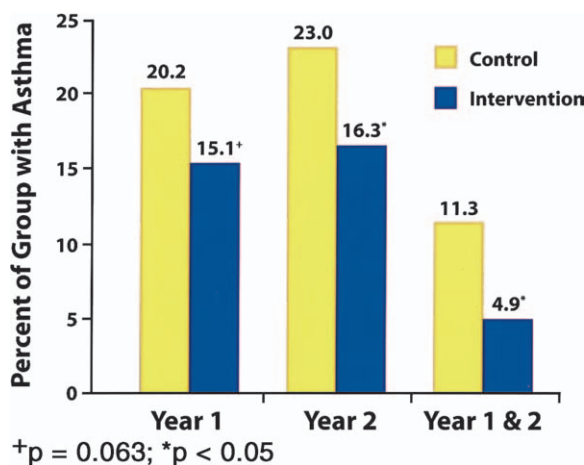


FIG 1. There is a trend toward a decrease in asthma at year 1 in the intervention group (blue bars) versus the control group (yellow bars). At year 2, there is a significant decrease in asthma in the intervention group. The major difference between groups is those children with persistent asthma (year 1 and 2), with significantly fewer in the intervention group than in the control group.

children without asthma (3.7%). Sensitization to cat was present in 2.1% of children and 0.6% each to dog, HDM, and cockroach. *Alternaria* species sensitivity was present in 1.5% of children, and *Cladosporium* species sensitivity was present in 0.4%. Among children with asthma, 3.8% were sensitized to cat, which was not significantly different from that seen in children without asthma. No children with asthma were sensitized to HDM at 2 years.

Risk factors associated with asthma and atopy at 2 years

There was no relationship between asthma at 2 years of age and family history of asthma, other allergies, or city of residence. Significantly more boys had asthma than girls (23.0% vs 15.8%, $P < .05$), as did children of mothers with higher education (25.7% vs 17.7%, $P < .05$). There was no difference in atopy for these factors.

Children with asthma at 2 years were more likely to have been exposed to maternal smoking during pregnancy and the first 12 months compared with those exposed to paternal smoking or others smoking or those not exposed to ETS (Table II).

Exposure to HDM or cat allergen at 2 µg/g dust or more did not influence the incidence of asthma at 2 years. Breast-feeding for more than 4 months was not associated with either decreased or increased risk for asthma by 2 years of age in these high-risk children. Similarly, daycare in the first year did not affect the incidence of asthma at 2 years. However, daycare at any time during the first 12 months of life was associated with less atopy at 2 years (5.0 % vs 15.4% not in daycare, $P < .05$, Table II).

Atopy at 12 months was predictive of asthma at 24 months. In particular, children sensitized to a food at 12 months were more likely to have asthma at 2 years (26.6% vs 17.7% not sensitized to food, $P < .05$).

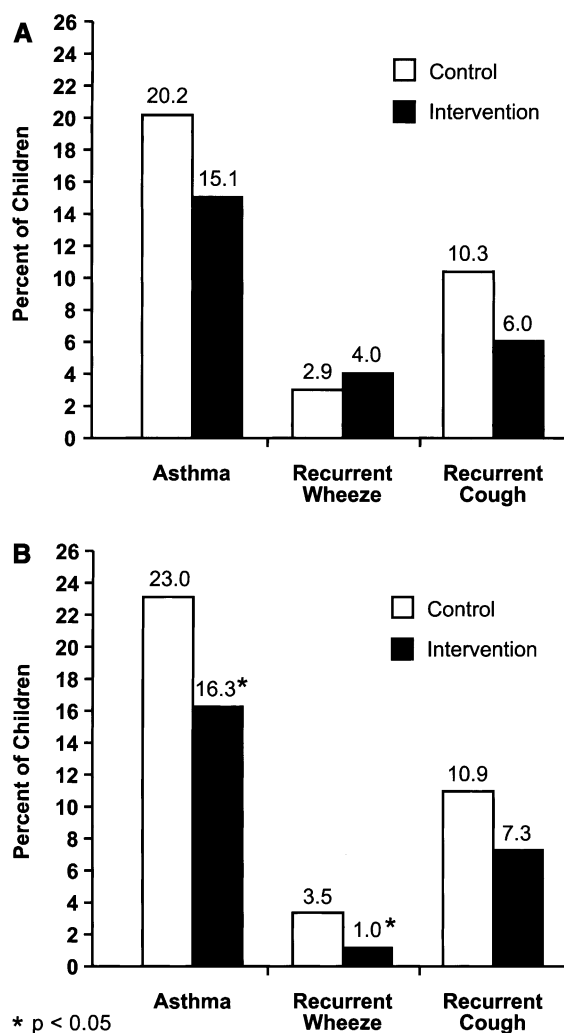


FIG 2. Asthma at 1 year (A) and 2 years (B) and recurrent wheeze and cough are shown for the intervention (solid bars) and control (open bars) groups. There is a significant decrease in asthma and recurrent wheeze at 2 years of age for the intervention group compared with the control group.

DISCUSSION

We have undertaken a prospective, randomized, controlled study of a multifaceted intervention designed to decrease exposure to allergens (both inhaled and ingested) and exposure to ETS in the first year of life of infants at high risk for asthma because of their family history. We previously reported a significant reduction in asthma in the intervention group at 12 months of age.¹⁶ We now report a significant difference in the prevalence of asthma at 2 years of age between the children in the intervention and control groups. For persistent asthma (ie, asthma present both at 12 months and 2 years of age), there was a 60% decrease in the intervention group. This is particularly important given the data demonstrating that most cases of asthma begin in early life.^{21,22}

TABLE II. Exposure in the first year of life and outcome at 2 years: Relationship of exposure to daycare during the first year of life, breast-feeding, and ETS, HDM, and cat allergen with asthma and atopy at 2 years

	Asthma, n = 93/476 (19.5%)	Atopy, n = 69/476 (14.5%)
ETS before delivery		
None	66/363 (18.2%)	54/363 (14.9%)
Father and others	13/77 (17.1%)	13/77 (17.3%)
Mother and others	14/36 (38.9%)*	2/36 (7.3%)
ETS postnatal 12 mo		
None	56/322 (17.4%)	49/322 (15.2%)
Father and others	18/99 (18.2%)	16/99 (16.3%)
Mother and others	19/55 (34.5%)*	4/55 (7.3%)
HDM exposure 12 mo		
<2 µg/g dust	83/400 (20.8%)	57/400 (14.3%)
≥2 µg/g dust	10/76 (13.2%)	12/76 (16.0%)
Fel d 1 exposure 12 mo		
<2 µg/g dust	70/346 (20.3%)	49/346 (14.2%)
≥2 µg/g dust	23/130 (17.7%)	20/130 (15.5%)
Breast-feeding		
No	9/39 (23.1%)	7/39 (17.9%)
<4 mo	18/68 (26.5%)	8/68 (11.8%)
>4 mo	66/369 (17.9%)	54/369 (14.6%)
Daycare during 12 mo		
No	84/435 (19.3%)	67/435 (15.4%)
Yes	9/41 (22.5%)	2/41 (5.0%)*

*Significant differences between exposure by χ^2 tests, $P < .05$.

The diagnosis of asthma in preschool children, particularly in infants, is a difficult problem. Asthma in the preschool child is a clinical diagnosis that, in recent years, has frequently given way to a diagnosis of "reactive airway disease."²³ Wheezing is a common phenomenon in early life and might occur in more than half of children.²³ In many children wheezing will resolve by school age, but in others it persists and eventually is recognized as asthma.²⁴ Data from the Tucson Cohort were analyzed to define an index predictive for children likely to have persistent asthma. The investigators defined a stringent clinical index for children with recurrent wheezing during the first 3 years of life that predicted subsequent asthma.²⁵ That stringent clinical index included either a parental history of asthma, the presence of allergic eczema in the child, or 2 of 3 "minor" criteria (eosinophilia, wheezing without colds, or allergic rhinitis).²⁵ These criteria are entirely consistent with the diagnosis of asthma that we used for our study. In all probability, the children in our study given a diagnosis of asthma, particularly those with asthma at both 1 and 2 years, are the "persistent wheezers" described in the Tucson Cohort,²⁴ as defined by the clinical index to predict asthma.²⁵ Because asthma is "primarily a wheezing disease" in preschool children²⁶ it is particularly of interest that our intervention had its greatest effect on recurrent wheeze, with a 90% reduction in the intervention group compared with that seen in the control group at 2 years. These data need to be confirmed once the children in our cohort are old enough for objective pulmonary function testing.

The Isle of Wight study by Hide et al,¹³ using intervention focused on HDM control and food avoidance in early life, reported a dramatic reduction in recurrent wheezing at 1 year in infants at high risk on the basis of an atopic background.¹¹ At 2 and 4 years, there was no longer any statistically significant difference for asthma between the intervention and control groups.^{12,13} At age 8 years, there was a significant decrease in nocturnal cough and atopy and a trend toward less asthma, as defined by wheeze and bronchial hyper-responsiveness (OR, 0.58; 95% CI, 0.18-1.86).²⁷ Lack of statistical significance after 1 year might reflect the smaller sample size of that study.

The Manchester Asthma and Allergy Study focused on decreasing exposure to HDM allergen in 291 families in which both parents were atopic, the mother was sensitized to indoor allergens, and there were no pets in the home.²⁸ The intervention was successful in decreasing exposure to HDM²⁸ and had a significant effect on attacks of severe wheeze with shortness of breath (relative risk, 0.44; 95% CI, 0.20-1.00) and prescriptions for wheezy attacks (relative risk, 0.58; 95% CI, 0.36-0.95) by 12 months of age.²⁹

Recent data from the Childhood Asthma Prevention Study in Australia found no benefit for active HDM avoidance intervention in high-risk infants at 18 months of age.³⁰ However, both our study and the Manchester Asthma and Allergy Study successfully decreased HDM to about 1.0 µg/g dust, more than 5 times lower than in the Childhood Asthma Prevention Study or Isle of Wight studies.

When we designed our study, the goal was to achieve a multifaceted intervention during the window of opportunity in the first year of life, with a focus on factors that previously had been associated with the development of asthma. A major focus of our study was successful for decreased HDM and cat allergen levels in the intervention homes.^{16,20} In our cohort exposure to HDM or cat of 2 µg/g or more, a risk factor noted by Sporik et al,⁵ was not associated with increased risk for asthma or atopy by 2 years. We cannot rule out the possibility that early exposure to high concentrations of allergens might be associated with increased risk for asthma later in childhood, as previously shown.⁵ Few children reacted on skin testing to HDM or cat at 2 years, and sensitization to any aeroallergen in children with asthma was only 6.5%. Recent studies suggest that exposure to cats or dogs in early childhood might be associated with decreased reduction in the incidence of allergy or asthma.³¹⁻³⁵ We did not find a significant protective nor enhancing effect of exposure to high levels of cat allergen in our study.

Another facet of our intervention program was to encourage breast-feeding and delay introduction of foods through the first year of life.¹⁶ A recent meta-analysis¹⁴ was encouraging in demonstrating that children who were breast-fed for at least 3 months had a 20% decrease in the risk for asthma.¹⁴ Similarly, a recent epidemiologic study suggested that introduction of milk other than breast milk

before 4 months of age was a risk factor for asthma in young children.¹⁵ In contrast to this, data from the Tucson cohort suggest that breast-feeding might lead to a higher prevalence of asthma in allergic children by 6 years of age.³⁶ Similarly, data from Dunedin showed an increased risk for asthma in a general population cohort with breast-feeding for 4 weeks or more.³⁷ In our study of children at high risk for asthma, breast-feeding was neither associated with protection nor an increased risk for asthma. There was a nonsignificant trend for a decreased risk for atopy among children with any breast-feeding. Also in our study, as with previous studies,⁷ children sensitized to food at 12 months were significantly more likely to have asthma at 2 years.

Atopy, as defined by a positive skin test response to inhalants allergens and food in early life, is predictive for development of asthma. Our multifaceted intervention did not significantly decrease the incidence of atopy in the intervention group at 2 years, although daycare in the first year of life was associated with less atopy. Whether daycare in early life will prove to be associated with less asthma when the children are older, as shown by Ball et al³⁸ in a general population cohort, is yet to be seen.

In conclusion, we undertook a multifaceted intervention focused on decreasing exposure to inhalant and ingested allergens and to ETS during the first year of life for children at high risk for the development of asthma. This intervention was effective in significantly reducing the incidence of asthma at 2 years of age. Although asthma at age 2 years was not related to sensitization to aeroallergens, atopy at 1 year of age was predictive for asthma at 2 years of age. Exposure to ETS in utero or during the first year of life are also important risk factors for asthma at 2 years of age. We believe that the symptom pattern for asthma we defined is consistent with a strong likelihood that these children will truly have persistent asthma into their later childhood. However, it will be important to reassess these children as they reach school age to determine whether our multifaceted intervention during a window of opportunity in the first year of life has been effective in decreasing the risk for development of chronic and persistent asthma in these children in later life.

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REFERENCES

1. Bjorksten B, Kjellman BN-IM, Zeiger RS. Development and prevention of allergic disease in childhood. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. *Allergy: principles and practice*. St. Louis: Mosby Yearbook; 1998. p. 816-37.
2. Manfreda J, Becker AB, Wang PZ, Roos LL, Anthonisen NR. Trends in physician-diagnosed asthma prevalence in Manitoba between 1980 and 1990. *Chest* 1993;103:151-7.

3. Dold S, Wjst M, von Mutius E, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis and atopic dermatitis. *Arch Dis Child* 1992;67:1018-22.
4. Platts-Mills TAE, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: report of the Third International Workshop. *J Allergy Clin Immunol* 1997;100(suppl):S2-24.
5. Sporik R, Holgate S, Platts-Mills T, Cogswell J. Exposure to house-dust mite allergen (Der p1) and the development of asthma in childhood. *N Engl J Med* 1992;323:502-7.
6. Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TAE. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude: tickling the dragon's breath. *Am J Respir Crit Care Med* 1995;151:1388-92.
7. Rhodes HL, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J Allergy Clin Immunol* 2001;108:720-5.
8. Weiss ST, Tager IB, Schenker M, Speizer FE. The health effects of involuntary smoking. *Am Rev Respir Dis* 1983;128:933-42.
9. Ehrlich RI, Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA, et al. risk factors of childhood asthma and wheezing: importance of maternal and household smoking. *Am J Respir Crit Care Med* 1996;154:681-8.
10. Murray AB, Morrison BJ. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J Allergy Clin Immunol* 1986;77:575-81.
11. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;339:1493-7.
12. Hide DW, Matthews S, Matthews L, Stevens M, Ridout S, Twiselton R, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. *J Allergy Clin Immunol* 1994;93:842-6.
13. Hide DW, Matthews S, Tariq S, Arshad SH. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996;51:89-93.
14. Peat JK, Li J. Reversing the trend: reducing the prevalence of asthma. *J Allergy Clin Immunol* 1999;103:1-10.
15. Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999;319:815-9.
16. Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. *Arch Pediatr Adolesc Med* 2000;154:657-63.
17. Chan-Yeung M, Ward H, Lam J, Ferguson A, Warren P, Simons E, et al. Mite and cat allergen levels in the homes and severity of asthma. *Am J Respir Crit Care Med* 1995;152:1805-11.
18. Luczynska C, Arruda L, Platts-Mills T, Miller J, Lopez M, Chapman M. A two-site monoclonal antibody ELISA for the quantification of the major *Dermatophagoides* spp. Allergens, Der p 1 and Der f 1. *J Immunol Methods* 1989;118:227-35.
19. De Blay F, Heyman P, Chapman M, Platts-Mills TAE. Airborne dust mite allergens: comparison of group II allergens with group I mite allergen and cat-allergen. *J Allergy Clin Immunol* 1991;88:919-26.
20. Chan-Yeung M, Ferguson A, Dimich-Ward H, Watson W, Manfreda J, Becker A. Effectiveness of and compliance to intervention measures in reducing house dust and cat allergen levels. *Ann Allergy Asthma Immunol* 2002;88:52-8.
21. Gergen PJ, Turkeltaub PC, Kramer RA. Age of onset in childhood asthma: data from a national cohort. *Ann Allergy* 1992;68:507-14.
22. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. *Am Rev Respir Dis* 1992;146:888-94.
23. Fahy JV, O'Byrne PM. Reactive airways disease. A lazy term of uncertain meaning that should be abandoned. *Am J Respir Crit Care Med* 2001;163:822-3.
24. Martinez FD, Wright AL, Taussig LM, Holbert CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
25. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
26. Strunk RC. Defining asthma in preschool-aged child. *Pediatrics* 2002;109:357-61.

27. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomized controlled study. *Thorax* 2003;58:489-93.
28. Custovic A, Simpson BM, Simpson A, Hallam C, Craven M, Brutsche M, et al. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. *J Allergy Clin Immunol* 2000;105:252-8.
29. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomized trial. *Lancet* 2001;358:188-93.
30. Mithrshahi S, Peat JK, Marks GB, Mellis CM, Tovey ER, Webb K, et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the childhood asthma prevention study (CAPS). *J Allergy Clin Immunol* 2003;111:162-8.
31. Roost H-P, Kunil N, Schindler C, Jarvis D, Chinn S, Perruchoud AP, et al. Role of current and childhood exposure to cat and atopic sensitization. *J Allergy Clin Immunol* 1999;104:941-7.
32. Svanes C, Jarvis D, Chinn S, Burney P, for the European Community Respiratory Health Survey. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;103:415-20.
33. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;108:509-15.
34. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6-7 years of age. *JAMA* 2002;288:963-72.
35. Celedon JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, et al. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. *Lancet* 2002;360:781-2.
36. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56:192-7.
37. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JC, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002;360:901-7.
38. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343:538-43.