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# Primary Prevention of Allergy and Asthma Is Possible

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**Abstract**

Allergic diseases, such as asthma, are the result of complex gene–environment interactions. The focus for prevention of allergic disease has been on environmental control. Environmental exposures begin during the intrauterine period, during which a T-helper-2 immune phenotype is promoted. Food allergy frequently occurs during the first year of life, and avoidance of exposure must begin in early pregnancy and must be complete to be effective. Partial avoidance strategies have not been successful. Current data do not allow us to specifically recommend breastfeeding for the prevention of allergy and allergic diseases, but for other important reasons, breastfeeding (particularly exclusive breastfeeding) should be encouraged for at least the first 4 mo of life. Sensitization to allergens is one of the strongest determinants for subsequent development of asthma. There is a strong relationship between exposure to house dust mites, allergen sensitization, and asthma. However, exposure to pets and animals in a farming environment early in life may actually be protective for the development of allergy and asthma. Specific recommendations relating to these exposures requires additional research, but genetics clearly plays an important role in that process.

To date, only a multifaceted intervention program has been successful as a primary prevention strategy for the development of asthma in young children. The specific components of the multifaceted intervention and the duration of protection have not yet been defined. It is increasingly clear that gene-directed environmental manipulation undertaken in a multifaceted manner during a "window of opportunity" is critical in the primary prevention of allergy and allergic diseases like asthma.

## Index Entries

Asthma; allergy; prevention; hygiene; children; immune response; lymphocytes; Th2; genetics.

## Heritability and Allergy

It has long been recognized that there is a strong heritable component for asthma and other allergy-associated diseases *(1)*. Data suggest that atopic children are at much greater risk than nonatopic children for the development of asthma *(2–5)*. Although there is a clear heritable contribution to allergic diseases, there is increasing awareness of the importance of gene–environment interactions in these complex diseases. Because of the rapid increase in prevalence of allergic diseases over the past 30 yr, it is difficult to ascribe the change to genetic alteration. Therefore, the focus for understanding the changing prevalence and attempting to prevent development of allergic diseases has predominately focused on the environment.

## The Interuterine Environment

The interuterine environment plays an important role in subsequent life processes, including allergic disease. There is a particularly important relationship between factors in pregnancy and development of allergic diseases. For example, there is a significantly increased risk for development of asthma associated with mothers younger than age 30 yr—and particularly mothers younger than age 21 yr *(6)*. Additionally, interuterine growth appears to have some influence on the potential for developing asthma. In one study, 28.2% of infants with head circumference of 37 cm or greater developed asthma, compared with only 9.1% of infants whose head circumference was less than 33 cm ($p < 0.0001$) *(7)*. Similarly, there is a fourfold likelihood of increased serum immunoglobulin E (IgE) in adults whose head circumference was 14 inches at birth, compared with those with a head circumference of 13 inches or less at birth *(8)*.

There is increasing evidence that successful pregnancy is a T-helper (Th)2 phenomenon. In murine studies, injection of interleukin (IL)-3 or cerebrospinal fluid enhances fetal survival and promotes intrauterine growth, whereas injection of IL-2, tumor necrosis factor-α, or interferon-γ (Th1 cytokines) leads to fetal destruction *(9,10)*. There is also clinical evidence (summarized in ref. *9*) that "pregnant women undergo immunological changes consistent with weakening of cell-mediated immunity and strengthening of humoral immunity." Mosmann and colleagues *(9)* suggested that the placenta acts as an immunoabsorbent that is capable of removing large amounts of antifetal antibody without damage, whereas cell-mediated immunity is not well-buffered by the placenta. They suggested that a healthy feto-placental unit primarily supports a humoral immune response and is responsible for driving this Th2 environment. These data support the contention that pregnancy is an obligate Th2 environment and that the infant's immune system is preferentially driven by Th2 cells at birth.

## Allergen-Specific Responses

Food allergies frequently occur during the first year of life, and exposure to food allergens almost certainly occurs *in utero*. In one study, specific cow's milk IgE was found in the cord blood of infants from allergic parents *(11)*. Another study found cow's milk (β-lactoglobulin)-specific T-cell proliferation in blood from newborns at risk for allergy (based on the family history) but not in blood from newborns in the control group *(12)*. In another study, blood from infants with allergic first-degree relatives was assessed for response to egg and beef (ovalbumin and bovine serum albumin [BSA], respectively) *(13)*. In this study, 35% of infants' T cells responded to ovalbumin and 29% responded to BSA. None responded to tetanus toxoid (to which they had not yet been immunized). Kondo et al. *(14)* found that umbilical cord T-lymphocyte proliferation to albumin exposure was the most sensitive predictor for the presence of allergy at age 1 yr. Prescott et

al. *(15)* observed umbilical cord blood mononuclear cell proliferation to ovalbumin exposure in 42% of subjects.

Intuitively, it is logical that there may be some form of fetal or newborn T-cell responsiveness to ingestant allergens to which the fetus is almost certainly exposed *in utero*. Sensitization to inhalant allergens becomes apparent after the second year of life (later than to food allergens; ref. *16*), but the risk for sensitization to some inhalant allergens appears to be increased by exposure during infancy. Sporik and colleagues *(17)* found a correlation between the risk for asthma at age 11 yr and exposure to house dust allergen at 12 mo: the higher the exposure, the greater the risk. Recently, several groups, including our own, have demonstrated lymphoproliferative responses in cord blood mononuclear cells to inhalant allergens, such as grass pollen, tree pollen, cat, and house dust mite (HDM) *(13,18–20)*. There are also data demonstrating that there is an increased risk for allergy to birch pollen in infants born just prior to the birch pollen season *(21)*.

## Can We Prevent Development of Allergy and Asthma?

Because exposure to allergens almost certainly begins *in utero*, there have been several studies that have attempted to decrease or avoid exposure to highly allergenic foods during pregnancy and/or during breastfeeding *(22–26)*. Most studies showed no impact of such allergen avoidance to various foods and the development of asthma, although two studies demonstrated a decreased incidence of atopic dermatitis *(22,23)*. Intuitively, it is logical that there may be fetal or newborn T-cell responsiveness to ingestant allergens to which the fetus is almost certainly exposed *in utero*. It is probable that the intervention programs—particularly those focused on foods—began too late during pregnancy to actually avoid early intrauterine exposure and subsequent development of sensitization.

Food allergen avoidance during the last trimester and early life has "failed to modify atopic disease at age 7 yr and, more specifically, after 2 yr," and ". . . the benefits of food allergy preventative efforts are of limited duration because of the frequent remission of food sensitization and food allergy in early childhood" *(27)*. Studies generally demonstrate that neither avoidance nor exposure to a large amount of milk or egg modifies the development of allergic disease *(23,25)*.

There has been a general bias in favor of breastfeeding as prevention against early childhood wheezing and subsequent development of asthma. However, recent studies have disputed these general assumptions.

A meta-analysis of the association between breastfeeding and asthma included 12 studies (of 41 reviewed) comprising more than 8000 children (average age: 4.1 yr) *(28)*. Overall, there was a protective effect of breastfeeding on diagnosed asthma and recurrent wheeze among those children with an atopic predisposition (odds ratio [OR] = 0.52, 95% confidence interval [CI] 0.35–0.79). Interestingly, the benefit was less pronounced in studies where subjects were followed past age 2 yr. Since that review, several more studies have examined this association among children less than age 6 yr at follow-up using either prospective *(29)* or cross-sectional *(30,31)* designs. Results are quite similar to those reported in the meta-analysis of Gdlalevich *(28)*; breastfeeding appears protective against wheezing syndromes early in life.

However, there have been two recent prospective general population cohort studies suggesting an association between breastfeeding and increased asthma *(32,33)*. Wright and colleagues *(32)*, reporting on the Tucson Childhood Respiratory Study, found an excess risk of asthma after age 6 yr with exclusive breastfeeding lasting for 4 mo or more (OR =

8.7, 95% CI 3.4–22.2). The effect was confined to children who were atopic at age 8 yr and whose mother had asthma. Notably, breastfeeding was protective against wheezing that occurred before age 2 yr. Sears and colleagues *(33)* reported on the Dunedin birth cohort, which was assessed children repeatedly from the age of 9 to 26 yr. Breastfeeding for 4 wk or longer was associated with an increased risk of both atopy and asthma. The odds ratio of breastfeeding for current asthma with bronchial hyperreactivity (BHR) at any time between the ages of 9 and 21 yr was 2.33 (95% CI 1.46–3.72) *(33)*.

In support of the findings of these two prospective studies, in a large cross-sectional study of more than 25,000 schoolchildren (ages 6–15 yr), Takemura and colleagues *(34)* found a small excess of asthma among those who were breastfed for 3 mo or longer (OR = 1.2, 95% CI 1.05–1.36). The effect size in this study was likely underestimated by including in the comparison group, subjects with some features suggesting asthma, and by misclassification of infant feeding habits. Infante-Rivard and colleagues *(35)* first reported a protective effect of breastfeeding on wheezing that required a visit to the emergency room at age 3 or 4 yr. On follow-up of these cases up to 6 yr later, breastfeeding was not associated with the risk of wheeze that persisted beyond age 4 yr *(36)*. Two further cross-sectional studies using the International Study of Asthma and Allergies in Childhood protocol found that either there was a trend to a protective effect of breastfeeding on wheeze among children ages 5 to 8 yr *(37)* or the risk of wheezing from lack of breastfeeding was only apparent among those children ages 7 to 14 yr who did not report asthma in the family *(38)*.

Oddy and colleagues *(39)* from Australia reported the study that is in most apparent disagreement with the cohort studies of Wright and Sears (from Arizona and New Zealand, respectively). The first report of their prospective cohort study found that intro-duction of milk (other than breast milk) before age 4 mo was associated with an increase in the cumulative incidence of wheeze and doctor-diagnosed asthma to age 6 yr, as well as the report of wheeze in the year prior to the sixth birthday *(39)*. Therefore, exclusive breast-feeding was again clearly protective of early wheezing syndromes and was also protective of wheezing between ages 5 and 6 yr. Also, in a follow-up report (and in contrast to the findings of Wright and colleagues), the association did not depend on the presence of asthma in the mother *(40)*.

Although there is debate regarding breastfeeding, the benefits are sufficiently clear to suggest that this information not be used to recommend against breastfeeding. Moreover, as suggested by Oddy et al. *(39)*, it appears that the introduction of foreign proteins such as cow's milk is the critical factor that may modify the protective effect of breastfeeding. In the Dunedin cohort *(33)*, most infants who were breastfed received formula supplement during their first few nights in the hospital. We have recently presented preliminary data from our Canadian Asthma Primary Prevention Study regarding sensitization to common food at age 7 yr *(41)*. In that multifaceted intervention study, mothers were encouraged to breastfeed for at least 4 mo and for the first year, if possible. Where breastfeeding was not possible, partially hydrolyzed whey formula was supplied for supplementation until age 12 mo. During the last trimester of pregnancy and during breastfeeding, we encouraged mothers to absolutely avoid peanuts and tree nuts and to decrease exposure to cow's milk and eggs as well as their products. There was no significant difference in sensitization to foods at age 1 yr. At age 2 yr, there were fewer children sensitized to egg in the control group ($p = 0.037$), and there was a trend for less sensitization to egg and peanut in the control group at age 7 yr. High-risk children frequently sensitize to common foods in infancy, but sensitization

often resolves to milk and egg. Partial food avoidance strategies in the third trimester and during breastfeeding are ineffective methods of preventing allergy and may enhance sensitization to food in high-risk children and cannot be recommended for the prevention of allergy *(41)*.

## Early Life Inhalant Allergen Exposure

There has been a strong focus on the importance of the role of inhalant allergen exposure in early life and subsequent development of asthma. Because of the worldwide importance of sensitization to HDMs and asthma, there has been a strong focus on attempts to decrease dust mite exposure. There is a clear relationship between exposure to HDMs and the subsequent sensitization to that allergen. Recent studies demonstrated that it is possible to achieve and maintain low levels of allergen exposure during pregnancy and in early life *(42)*. Simple interventions, such as mattress encasements, have been demonstrated to decrease sensitization to HDMs in infants *(43)* with atopic dermatitis. However, in that study, infants had already developed evidence of atopy with sensitization to foods and the development of atopic dermatitis.

## Exposure to Pets and the Risk for Allergy and Asthma

Sensitization to allergens is one of the strongest determinants for subsequent development of asthma. Studies have demonstrated a relationship between HDM allergen exposure and sensitization, as well as between sensitization and asthma *(44–47)*. Several recent studies have raised the issue regarding whether a presence of a cat or dog in the home might decrease the risk of developing allergy to those allergens *(48–51)*. Several theories have been suggested to explain the observed phenomena, and numerous studies have recently been undertaken.

Two systematic reviews on this subject were published in 1998 *(52)* and 2001 *(53)*, and a recent publication reviewed specific studies published from 1991 to 2002 *(54)*. The authors of the latter publication noted that studies "are heterogeneous both in design and in results: some include exposure to birds and rodents, some are of high-risk children only, some look at early life exposure, and many have not measured allergic sensitization—all of which makes it difficult to determine common themes" *(54)*.

Apelberg and colleagues' *(53)* review of literature through 1999 found 32 of 217 articles that fulfilled their eligibility criteria. Their pooled risk estimates for asthma and wheezing showed a small increased risk associated with early life exposure to pets limited to studies with a study population age greater than 6 yr. Their overall study demonstrated an odds ratio of 1.11 for asthma (95% CI 0.98–1.25) and 1.19 for wheezing (95% CI 1.05–1.35) with pet exposure. They concluded that exposure to pets appeared to increase the risk of asthma and wheezing in older children, but noted that a somewhat lower (nonsignificant) risk among younger children could relate to a protective effect but could also be explained by selection bias.

There is a theme throughout the studies that must be clarified. If we are considering primary exposure of allergy and asthma, then we must consider exposure in early life, preferably focused on the first year of life. A Nordic interdisciplinary review of the scientific literature concerning the relationship between the exposure to pets at home, sensitization, and the development of allergy published in 1998 (NORDPET; ref. *52*) reviewed 1200 articles, 89 of which were selected for further study. They focused on exposure to pets in infancy and defined an increased relative risk (relative risk [RR] = 1–1.5) for sensitization but no significant impact on the development of symptoms.

Lau and colleagues *(47)* suggested that "the induction of specific IgE responses and the development of childhood asthma are deter-

mined by independent factors"—that is, they noted a relationship between sensitization to indoor allergens with asthma but no relationship between indoor allergen exposure and the presence of asthma or airway hyperresponsiveness in children at age 7 yr. They suggested that development of allergy and development of asthma are parallel events. This comment evoked responses in letters to the editor, one of which *(55)* stated that "the results could be interpreted as evidence that exposure to early life indoor allergens induces sensitization and causes the onset of asthma directly in children, which disputes the conclusion they made in their report." In a recent publication from the National Health and Nutrition Examination Survey (NHANES) III by Lanphear and colleagues *(56)* studying 5384 children ages 6–16 yr demonstrated a significantly increased odds ratio for the history of allergy to a pet and physician-diagnosed asthma (OR = 2.4, 95% CI 1.7–3.3). The current presence of a pet in the household in that study was also associated with an increased odds ratio for asthma (OR = 1.5, 95% CI 1.1–2.1).

Furthermore, Melén and colleagues *(57)* demonstrated that the risk for having current severe asthma at age 4 yr was associated with numerous risk factors, including exposure to high levels of cat allergen (Fel d 1 > 8 μg/g of dust), as well as to parental smoking during the first 2 yr of life. In contrast, Platts-Mills and colleagues *(58)* carefully studied the immune response among 226 children, 47 of whom had asthma and airway hyperresponsiveness. They demonstrated that increasing exposure to HDMs was associated with increased prevalence of sensitization to the HDM but that the highest exposure to cat was associated with decreased sensitization and a higher prevalence of IgG antibody to Fel d 1. Nevertheless, in that study, sensitization to mite and cat allergens was the strongest independent risk factor for asthma ($p < 0.001$).

Thus, although some debate exists regarding increased exposure and sensitization, it is clear that sensitization (at least to cats and HDMs) is a significant risk factor for asthma. Therefore, the question is twofold: (a) do the data support an increased or decreased risk for sensitization to pets with pet exposure? and (b) do the data support an increased likelihood of developing asthma with increased pet exposure independent of allergy? Furthermore, we must address an important confounder regarding whether the removal of pets from homes of families with a high risk for developing allergy and asthma plays a role in this process.

## Does Early Exposure to Cat or Dog Protect Against Later Allergy Development?

This question was posed in one of the early studies demonstrating a decreased frequency of positive skin tests in children at age 12 to 13 yr, when they had been exposed during the first year of life to cats *(48)*. This study also demonstrated a lower frequency of allergic rhinitis at ages 7 and 9 yr and of asthma at ages 12 to 13 yr. The study enrolled 1649 children at ages 7 to 9 yr and re-assessed the children at ages 12 to 13 yr. The history of pet ownership during the first year of life was obtained at the initial visit at ages 7 to 9 yr. The authors concluded that "pet exposure during the first year of life and increasing the number of siblings were both associated with a lower prevalence of allergic rhinitis and asthma in schoolchildren." This was followed by two studies from the European Community Respiratory Health Survey *(49,50)*, both of which demonstrated significantly decreased sensitization to cats in young adults if there had been "childhood exposure" to pets. This occurred despite the fact that those who owned cats were significantly more likely to be sensitized to cats than those who did not (OR = 1.57, 95% CI 1.20–2.06). One of these studies *(49)* demonstrated a significant negative relationship between adult atopy, family size, and the presence of a dog in the home during childhood (OR = 0.85, 95% CI 0.78–0.92). The presence of a cat in the home during childhood had no impact unless there

was parental allergy, in which case there was a significant decreased likelihood for atopy with the presence of a cat in the home during childhood (OR = 0.86, 95% CI 0.76–0.89). Since this study, there have been numerous additional studies that specifically considered development of atopy. There was a wide range of outcomes for early life exposure to pets and atopy. This included no change in sensitization risk (two studies; refs. *59* and *60*), decreased risk for atopy with "furred pets during childhood" (one study; ref. *61*), dogs in the first year of life and decreased sensitization to pollen (one study; ref. *62*), and two or more cats and dogs in the first year of life and atopy at age 6 to 7 yr (one study; ref. *51*). It has been suggested that the "inverse association between current pet ownership and sensitization and hay fever symptoms partly resulted from removal of pets in families with sensitized and/or symptomatic children. Pet ownership in the first 2 yr of life only appeared to offer some protection against sensitization to pollen."

An important consideration is the presence of the pet in the home in early life vs current exposure. Considering early life exposure for wheezing/asthma, including exposure through the first 5 yr of life, provides two publications since 1999 that demonstrated no significant difference *(63,64)*. Two studies demonstrated a decreased risk for wheezing/asthma *(65,66)*; one of these studies stratified for children with a maternal history of asthma demonstrated an increased risk of wheezing *(66)*.

Nafstad and colleagues *(63)* followed a population-based cohort of 2531 children born in Oslo, Norway, from birth to age 4 yr. Exposure to pets in early life was associated with a nonsignificant trend for decreased asthma at age 4 yr (OR = 0.7, 95% CI 0.5–1.1). They noted that "these findings might also be explained for selecting to keep pets." Hölscher and colleagues *(64)* performed a questionnaire with children from the former East Germany ($n$ = 7611 questionnaires from 5360 different children examined between 1992 and 1999). They noted a nonsignificant inverse association between contact with dogs during the first year of life and lifetime prevalence of asthma (OR = 0.68, 95% CI 0.43–1.08).

Litonjua and colleagues *(65)* followed 226 children younger than 5 yr old for 4 yr. Exposure to cat allergen and the presence of a dog in the home were both associated with a decreased risk for wheezing. The odds ratio for the presence of a dog in the home (using a multivariate analysis model) was 0.34 (95% CI 0.12–0.98). For Fel d 1 concentrations of 1 μg/g or more, the odds ratio for wheezing was 0.61 (95% CI 0.37–1.01).

Celedón and colleagues *(66)* followed 448 children who had at least one parent with a history of atopy from birth to age 5 yr. For the entire cohort, there was a trend for an inverse association between exposure to a cat and wheezing in the first 5 yr of life (RR = 0.7, 95% CI 0.5–1, $p$ = 0.08). However, there was a significant interaction between exposure to a cat and maternal history of asthma ($p$ = 0.004). Among children whose mother had no history of asthma, exposure to a cat at age 2 mo was associated with a significantly reduced risk of wheezing between ages 1 and 5 yr (RR ~ 0.6 over 5 yr). However, among children whose mothers had a history of asthma, exposure to a cat at age 2 mo was associated with a significantly increased relative risk for asthma by age 3 yr, which progressively increased to through age 5 yr.

The Childhood Origins of Asthma Study *(67)* enrolled prospective parents of whom either the mother or father had a history of allergic rhinitis, asthma, or both. In this study, exposure to a dog in infancy was associated with less allergen sensitization and atopic dermatitis at age 1 yr. The risk for atopic dermatitis was influenced by a genotypic single nucleotide polymorphism (SNP) in the promoter region of the receptor for lipopolysaccharide endotoxin (CD14 C–159 T). Infant homozygous for the SNP (–159 TT) were less likely to have atopic dermatitis at 1 yr if they

were exposed to a dog (5 vs 43%) *(67)*. Similarly, Bavarian children raised on animal farms demonstrated less allergy and asthma, likely as a result of endotoxin exposure *(68)*. In those children, a genetic variation in toll-like receptor 2 (which is important for the response to many cell membrane factors from a wide range of bacteria) was a major determinant for the susceptibility to asthma and allergy in those farm children *(69)*.

## Multifaceted Intervention for Primary Prevention of Allergy and Asthma

Sensitization to aero-allergen *(44,70,71)*, allergy to foods (particularly to egg; ref. *72*), and exposure to environmental tobacco smoke *(73–75)* early in life are all major risk factors for asthma. There is increasing recognition that approaches to primary prevention must be multifaceted. Unfortunately, to date, there are limited data from prospective, randomized, controlled studies regarding the primary prevention of asthma. The Isle of Wight Study by Hide et al. *(76)* using intervention focused on HDM control and food avoidance in early life reported a dramatic reduction in recurrent wheezing at 1 yr in infants at high risk (on the basis of an atopic background). At 2 and 4 yr, there was no longer a statistically significant difference for asthma between the intervention and control groups *(77,78)*. At age 8 yr, there was a significant decrease in nocturnal cough and atopy and a trend toward less asthma as defined by wheeze and BHR (OR = 0.58, 95% CI 0.18–1.86; ref. *79*). Lack of statistical significance after 1 yr may be reflective of the smaller sample size of that study.

A more recent study, the Manchester Asthma and Allergy Study (MAAS), 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 *(80)*. The intervention was successful in decreasing exposure to HDM *(80)* and had a significant effect on

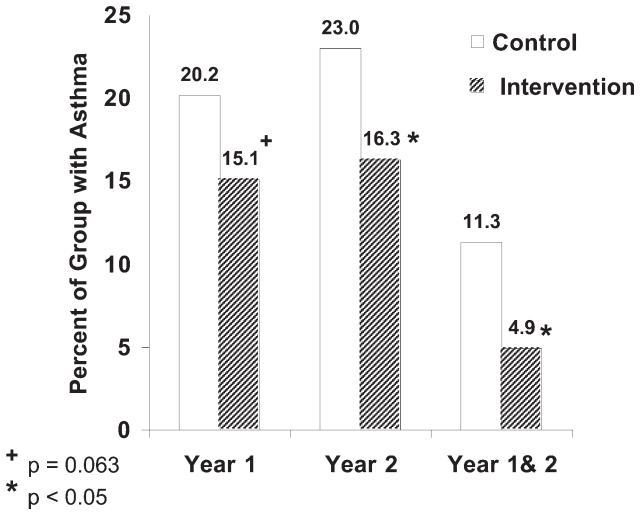


Fig. 1. There is a trend to decrease in asthma at year 1 in intervention (shaded bars) vs control (open bars) at year 1. At year 2, there is a significant decrease in asthma in the intervention group. The major difference between groups is those children with persistent asthma (years 1 and 2) with significantly fewer in the intervention group compared with the control group. (From ref. *84*.)

attacks of severe wheeze with shortness of breath (RR = 0.44, 95% CI 0.20–1) and prescriptions for wheezing attacks (RR = 0.58, 95% CI 0.36–0.95) by age 12 mo *(81)*.

Recent data from the Childhood Asthma Prevention Study (CAPS) in Australia found no benefit for active HDM avoidance intervention in high-risk infants at age 18 mo *(83)*. However, both our multifaceted Canadian Asthma Primary Prevention Study and the MAAS successfully decreased HDM to about 1 μg/g of dust—more than five times lower than the CAPS or Isle of Wight studies.

When we designed our Canadian Primary Prevention 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 had previously been associated with the development of asthma. We reported a significant difference in the prevalence of asthma at age 2 yr between the children in the intervention and control groups. For persistent asthma (i.e., asthma present both

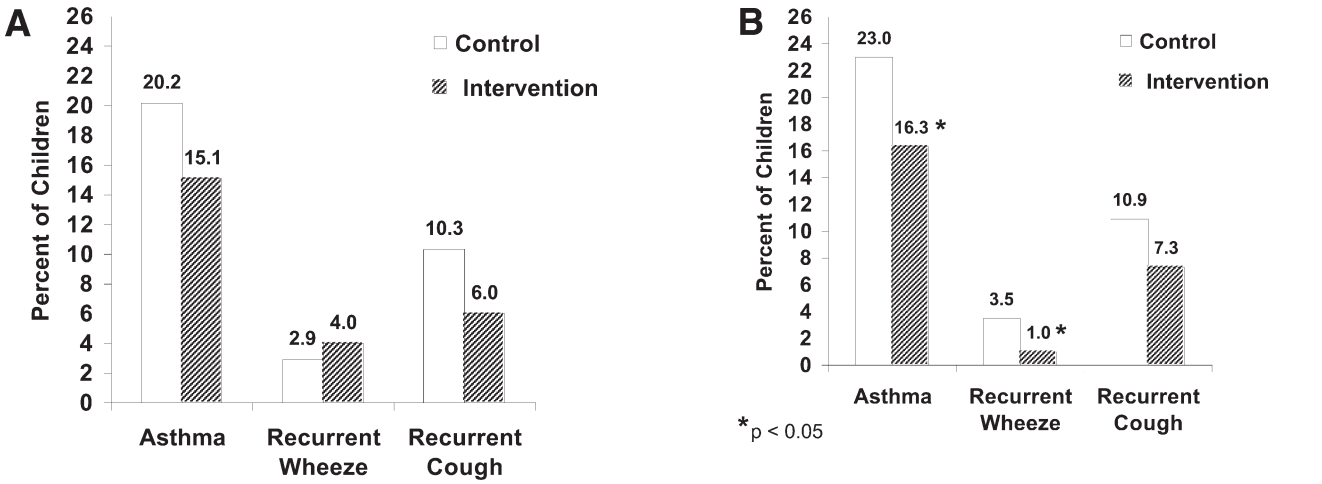


Fig. 2. Asthma at 1 yr **(A)** and 2 yr **(B)** and recurrent wheeze and cough are shown for intervention (shaded bars) and control (open bars) groups. There is a significant decrease in asthma and recurrent wheeze at age 2 yr for the intervention group compared with the control group. (From ref. *84*.)

at age 12 mo and 2 yr), there was a 60% decrease in the intervention group (Figs. 1 and 2; ref. *84*). A major focus of our study was successful for decreased HDM and cat allergen in the intervention homes *(82,85)*. In our cohort, exposure to 2 μg/g or more of HDM or cat (a risk factor noted by Sporik et al. *[17]*) was not associated with increased risk for asthma or atopy by 2 yr. We cannot rule out the possibility that early exposure to high concentrations of allergens may be associated with increased risk for asthma later in childhood, as previously shown *(17)*. Few children reacted to HDM or cat on skin testing at 2 yr, and sensitization to any aero-allergen in children with asthma at that age was only 6.5%. Recent studies suggest that exposure to cats or dogs in early childhood may be associated with a reduction in the incidence of allergy or asthma *(49–51,60,66)*. We did not find a significant protective or an enhancing effect of exposure to high levels of cat allergen in our study (Table 1).

Another facet of our intervention program was to encourage breastfeeding and delay introduction of foods throughout the first year of life *(82)*. In our study of children at high risk for asthma, breastfeeding was neither associated with protection nor an increased risk for asthma. There was a nonsignificant trend for a decreased risk of atopy among children with any breastfeeding. In our study, and in previous studies *(72)*, children sensitized to food at 12 mo were significantly more likely to have asthma at 2 yr of age (Table 1; ref. *84*).

Atopy, as defined by a positive skin test to inhalant allergens and food in early life, is predictive for the development of asthma. Our multifaceted intervention did not significantly decrease the incidence of atopy in the intervention group at 2 yr, although daycare in the first year of life was associated with less atopy (Table 1; ref. *84*). It has yet to be seen whether daycare in early life will prove to be associated with less asthma when the children are older, as shown by Ball et al. in a general population cohort *(86)*.

A recent Swedish observational study monitored almost 4000 children up to age 2 yr and assessed their families' compliance with the Swedish National Allergy Preventative Guidelines. They noted that "compliance with the Swedish National Allergy Preventative Guidelines, deliberate or not, was associated with recurrent wheezing in 12.6% of the children, compared with 24.1% of the children exposed to at least two of these three factors:

Table 1
Exposure in First Year of Life and Outcome at 2 yr.

| | Asthma $n = 93/476$ (19.5%) | Atopy $n = 69/476$ (14.5%) |
|---|---|---|
| ETS before delivery | | |
| None | 66/363 (18.2%) | 55/363 (15.2%) |
| Father and others | 13/77 (17.1%) | 13/77 (17.3%) |
| Mother and others | 14/36 (38.9%)[a] | 2/36 (7.3%) |
| ETS postnatal 12 mo | | |
| None | 56/322 (17.4%) | 50/322 (15.6%) |
| Father and others | 18/99 (18.2%) | 16//99 (16.3%) |
| Mother and others | 19/55 (34.5%)[a] | 4/55 (7.3%) |
| HDM exposure 12 mo | | |
| <2 μg/g of dust | 83/400 (20.8%) | 58/400 (14.6%) |
| ≥2 μg/g of dust | 10/76 (13.2%) | 12/76 (16%) |
| Fed d1 exposure 12 mo | | |
| <2 μg/g of dust | 70/346 (20.3%) | 50/346 (14.5%) |
| ≥2 μg/g of dust | 23/130 (17.7%) | 20/130 (15.5%) |
| Breastfeeding | | |
| 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%) | 55/369 (15%) |
| Daycare during 12 mo | | |
| No | 84/435 (19.3%) | 68/435 (15.7%) |
| Yes | 9/41 (22.5%) | 2/41 (5%)[a] |

[a]Significant differences between exposure by Chi-square tests; $p < 0.05$.
ETS, environmental tobacco smoke; HDM, house dust mite.
Relationship of exposure to ETS, house dust mite, and cat allergen, daycare during the first year of life and breastfeeding with asthma and atopy at 2 yr. (From ref. *84*.)

maternal tobacco smoke, being raised in a damp home, and breastfeeding for less than 4 mo. The corresponding figures for asthma were 6.8 and 17.9%, respectively" *(87)*. Of course, this was self-selected compliance. The authors concurred that the prevention or postponement of the onset of wheezing and asthma by simple preventative measures appears desirable *(87)*.

## Conclusion

Successful interventions designed for the primary prevention of allergy are possible; however, in the future, these interventions will need to be based on a better understanding of gene–environment interactions. Avoidance measures, particularly for food, have the potential to be effective but must be complete and introduced early in pregnancy. Therefore, this approach is not likely to be practical. For many reasons, breastfeeding should continue to be encouraged but cannot presently be promoted for the purpose of allergy prevention. Our multifaceted intervention program, which focuses on decreasing exposure to inhalant and ingestant allergens, as well as to environmental tobacco smoke in the "window of opportunity" during the first year of life for children at high risk for the development of asthma, has the potential to be protective. Our Canadian Asthma Primary Prevention Study intervention was effective in significantly reducing the incidence of asthma at age 2 yr. Exposure to environmental tobacco smoke *in utero* or during the first year of life remains an important

risk factor for asthma at age 2 yr. We believe that the symptom pattern for asthma defined in our study is consistent with a strong likelihood that these children will truly experience persistent asthma into later childhood. However, it will be important to re-assess children as they reach school age to determine whether a multifaceted intervention during a "window of opportunity" during the first year of life can be effective in decreasing the risk for development of chronic and persistent asthma in these children in later life. It is increasingly clear that gene-directed environmental manipulation undertaken in a multifaceted manner during a "window of opportunity" will be critical in the primary prevention of allergy and allergic diseases such as asthma.

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