

Letter to the Editor

Atopy in early life and effect of a primary prevention program for asthma in a high-risk cohort

To the Editor:

It is well known that both genetic and environmental risk factors are involved in the pathogenesis of asthma. There is considerable evidence that environmental exposures are important in early life because the immune system of infants has not yet fully developed, and intervention during this window of opportunity has been advocated to provide the maximal benefit for any asthma prevention program.¹

In 1995, we began a prospective, randomized, controlled study to determine the effectiveness of a multifaceted intervention program for the primary prevention of asthma in high-risk infants, defined as infants with at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases, identified during the mothers' third trimester of pregnancy.²⁻⁴ Families were recruited in 2 centers—Winnipeg and Vancouver, Canada—and randomly allocated to the intervention group (N = 279) or to the control group (N = 266) before the child's birth. The intervention measures, initiated shortly before birth and applied only during the first year of life, included avoidance of house dust mites, pets, and environmental tobacco smoke, encouragement of breast-feeding, and delayed introduction of solids.

The children were assessed for asthma at the ages of 1, 2, and 7 years by a pediatric allergist in each center using a structured questionnaire interview. Skin testing to common food and inhalant allergens was also performed. The intervention measures as a whole were effective in reducing the prevalence of asthma at each assessment; however, these measures did not reduce the prevalence of atopy, defined as positive skin testing to any of the allergens tested at any time or bronchial hyperresponsiveness at age 7 years.²⁻⁴ The discrepant finding of the effects intervention measures on asthma and atopy was particularly surprising. The purpose of this analysis was to determine to what extent atopic status at age 1 year (the end of our active intervention) was related to the later development of atopy and asthma at 7 years to study the interrelationships among the intervention, atopy, and asthma.

At 7 years of age, 380 children (70% of the original cohort) returned for assessment, and 363 children had skin testing. The children were grouped according to their atopic status as follows: atopic at ages 1 and 7 years (early, persistent atopy), atopic at age 1 year but not at 7 years (early, transient atopy), nonatopic at age 1 year but atopic at age 7 years (late-onset atopy), and nonatopic at ages 1 and 7 years (nonatopic; Fig 1). The prevalences of asthma at age 7 years in these groups were 51.7%, 7.7%, 20%, and 9.3% respectively.

Compared with nonatopic children, those with early, persistent atopy had a significant increased risk of asthma (adjusted odds ratio [OR], 15.5; 95% CI, 1.02-34.3)

adjusted for sex, maternal history of asthma, city of residence, dog ownership, and intervention group allocation (variables found to be significantly associated with asthma in this cohort by univariate analysis); children with late-onset atopy also had an increased risk of asthma (adjusted OR, 2.25; 95% CI, 1.07-4.73).

Our intervention measures during the first year of life resulted in a 4-fold reduction in the risk of asthma (adjusted OR, 0.26; 95% CI, 0.08-0.88) in the children who had not developed atopy by 1 year of age, but did not reduce the risk of asthma (adjusted OR, 0.68; 95% CI, 0.20-2.22) in children with early, persistent atopy even after adjustment for personal and family characteristics and exposure variables (Fig 1). For children in the control group who had not developed atopy at age 1 year, there was no corresponding reduction in the development of asthma at age 7 years.

The intervention measures did not reduce the risk of atopy at 7 years (OR, 1.35; 95% CI, 0.89-2.03), with the prevalence of atopy 49.0% in the intervention and 41.6% in the control group.

There were no significant differences in the personal and family characteristics between the different atopy groups, in particular for maternal, paternal, or biparental history of asthma or other allergies, which suggests that the early, persistent atopic children did not have a stronger hereditary component. Moreover, there were no significant differences in any of the exposure variables such as exclusive breast-feeding for at least 4 months, day care attendance, respiratory viral infections, cat or dog ownership, exposure to house dust mite allergen, or parental smoking. However, the prevalence of atopic dermatitis at age 1 year was significantly higher in children with early, persistent atopy (21.7%) than the late-onset atopy (6.7%) and nonatopic children (6.4%). At year 7, the prevalence of atopic dermatitis remained highest in children with early, persistent atopic (25%) compared with the other 2 groups (16.2% and 8.7%, respectively).

This study shows that our intervention measures were highly effective in preventing asthma in children in this high-risk cohort who had not developed atopy by age 1 year by decreasing the rates of asthma symptoms such as wheeze and not through an allergic/atopic mechanism. Another striking finding of this study is the very high prevalence of asthma at age 7 years in children with early, persistent atopy. This subgroup of children was at high risk of developing asthma and atopic dermatitis as part of the "atopic march" regardless of our intervention program. Therefore, being atopic by age 1 year appears to be an extremely important marker for subsequent development of asthma.⁵⁻⁷

We have not been able to identify which environmental exposure could explain the results. Because our study was designed to determine the effectiveness of a multifaceted intervention program, the sample size based on such a study design does not permit us to determine which

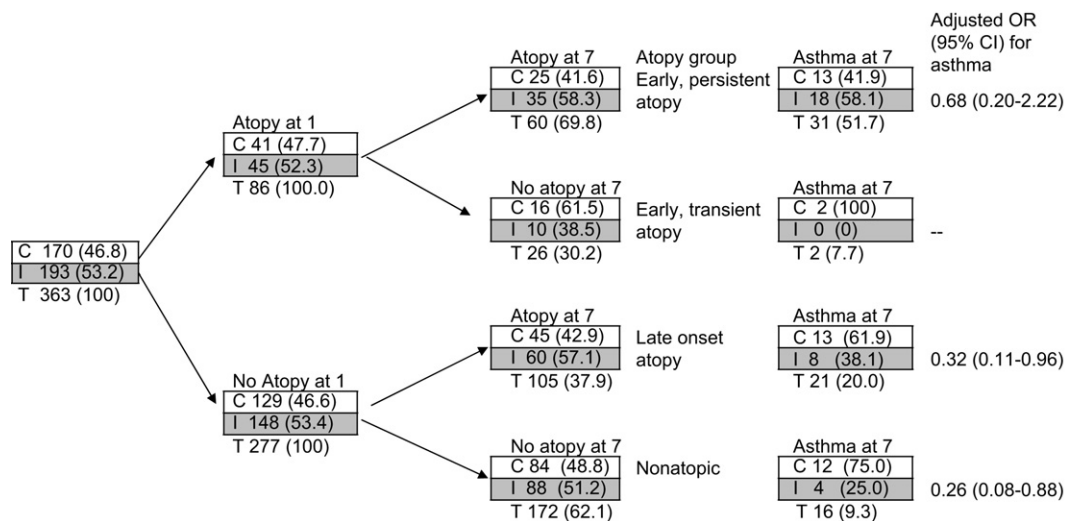


FIG 1. Outcome of children with and without atopy at age 1 year. *Comparison of control and intervention groups for asthma adjusted for sex, city of residence, maternal history of asthma, and dog ownership during year 1 (variables found to be significantly associated with asthma by univariate analysis). C, Control group; I, intervention group; T, total (% of total).

component of the intervention program was useful. As well, it is possible that prenatal exposures may affect on the immune system and lung development and influence expression of disease postnatally. Our finding of the differential effect of intervention measures on asthma and atopy suggests that the pathogenesis of asthma is different from that of other atopic disorders. However, because of the relatively small sample of high-risk children studied, these observations should be confirmed in a larger population-based cohort. Genetic studies may help define better the factors critical to this process among those children who have a strong immediate family history of asthma and atopy.

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