A Randomized Controlled Study on the Effectiveness of a Multifaceted Intervention Program in the Primary Prevention of Asthma in High-Risk Infants

Moira Chan-Yeung, MB; Jure Manfreda, MD; Helen Dimich-Ward, PhD; Alexander Ferguson, MD; Wade Watson, MD; Allan Becker, MD

Background: The prevalence of asthma has increased in developed countries in the past 2 decades. The effectiveness of intervention measures on the primary prevention of asthma has not been well studied.

Objective: To assess the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants (in this study, infants are defined as persons from birth to the age of 1 year).

Design: Prospective, prenatally randomized, controlled study with follow-up through the age of 1 year.


Participants: A total of 545 high-risk infants (at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases) identified before birth.

Interventions: Avoidance of house dust mite and pet allergens and environmental tobacco smoke, encouragement of breastfeeding, and supplementation with a partially hydrolyzed formula.

Main Outcome Measures: Probable or possible asthma, rhinitis without apparent colds, and a prick skin test result positive for common inhalant allergens.

Results: Thirty-eight (15.1%) of the 251 infants available for assessment in the intervention group and 49 (20.2%) of the 242 infants available for assessment in the control group fulfilled the criteria for possible or probable asthma (adjusted relative risk, 0.66; 90% confidence interval, 0.44-0.98). Also, 16.7% of the infants in the intervention group and 27.3% of the infants in the control group developed rhinitis without colds (adjusted relative risk, 0.51; 90% confidence interval, 0.35-0.74). The incidence of positive skin test results to 1 or more inhalant allergens was similar in both groups (4.4% in the intervention group and 4.6% in the control group).

Conclusions: Our multifaceted intervention program resulted in a modest but significant ($P = .04$) reduction in the risk of possible or probable asthma and rhinitis without apparent colds at the age of 12 months in high-risk infants. In the absence of a validated definition of asthma at the age of 12 months, follow-up studies are needed to determine the effectiveness of the intervention program in the primary prevention of asthma in high-risk infants.


During the past 2 decades, there has been an increase in the prevalence of asthma in developed countries. The increase in prevalence is associated with an increase in hospitalization for asthma and an increase in the sales of antiasthma medications. In 1990, the direct and indirect cost of treating asthma in the United States was $6 billion. Asthma is an environmentally induced lung disease in genetically predisposed individuals. The rapid increase in the prevalence of asthma during the past 3 decades suggests genetic mutation is unlikely to be the cause. Exposure to indoor allergens, such as house dust mites and pets, and exposure to environmental tobacco smoke have been shown to be important environmental risk factors for asthma. Reduced exposure to house dust mites as a result of avoidance measures is associated with improvement of asthma in children. However, the effectiveness of these measures in the primary prevention of asthma is less well studied.

To our knowledge, there has been only one prospective, randomized, controlled study on the primary intervention of asthma in high-risk infants. Environmental control measures showed a significant protective effect at the age of 12 months but not at the ages of 2 and 4 years. The results of 2 nonrandomized controlled studies were favorable. Other studies mainly assessed the effectiveness of breastfeeding and food allergen avoidance on allergic diseases. The results of these studies have been contradictory, with some showing a reduction in recurrent wheeze or asthma and others showing no effect.
PARTICIPANTS AND METHODS

PARTICIPANTS

High-risk infants, defined as those with at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases, were identified in prenatal clinics. Based on these criteria, using a short questionnaire, 641 women were identified as eligible in Vancouver from 2278 who were registered to give birth at a community-based maternity hospital; 271 (42.3%) were enrolled in the study. In Winnipeg, 428 were identified as eligible from 1473 women attending university-based antenatal clinics in offices of obstetricians; 274 (64.0%) were enrolled. The reasons for not participating included refusal, a language problem, delivery of the infant before the time of contact, premature delivery of the infant, and a change of residence. A research nurse explained the purpose of the study to eligible women during the prenatal visit. Informed consent was obtained from those willing to participate.

A computer-generated list of random numbers was used to determine group allocation separately for each center. A statistician placed the group allocation for each identification number in a sealed envelope. In total, 278 mothers were randomly allocated to the intervention group and 267 to the control (usual care) group. Seven families dropped out after the birth of the infants because of the poor health of the infants. By the end of 12 months of follow-up, an additional 49 families had dropped out from the study for various reasons, equally distributed between the control and intervention groups. There were 4 pairs of twins, 2 in the control group and 2 in the intervention group. Thus, 242 infants in the control group and 231 in the intervention group were available for assessment (Figure 1).

BASELINE ASSESSMENTS

Home visits were carried out before the birth of the infant and at 2 weeks and 4, 8, and 12 months after birth. The following procedures were carried out.

Questionnaires

The asthma questionnaire, a modified version of the European Community Respiratory Health Survey, was administered prenatally before randomization by a trained research nurse separately to the mother and father. During subsequent home visits, a brief questionnaire on the infant’s health and environment was administered.

Assessment of Home Characteristics

The homes were assessed using a questionnaire and a walkthrough survey during each visit. The age and type of the home; the number of occupants; the presence of water damage; leaks and dampness; mildew and molds; and the type of heating, fuel, and air control appliances used were recorded. Which household members smoked and the number and type of household pets were determined. For those infants who had to be placed in day care facilities, specific characteristics of these facilities were recorded.

House Dust Sampling

Dust samples were collected from 6 sites: the infant’s bedroom floor and mattress, the parents’ bedroom floor and mattress, the floor of the most commonly used room in the house, and the upholstered furniture in that room. A standard protocol was used for dust collection, as described previously. The samples were placed in a zip-locked bag and stored at −20°C until being extracted and analyzed for house dust mite and cat allergens. The levels were determined using an enzyme-linked immunosorbent assay with purified monoclonal antibodies against group 1 mite allergens, Dermatophagoides pteronyssinus and Dermatophagoides farinae, and cat allergen, Felis domesticus. All samples were determined in duplicate. The total mite allergen (sum of D pteronyssinus and D farinae) was reported in micrograms per gram of dust. The allergen levels of all 6 sites at each time were averaged in this presentation.

INTERVENTION PROGRAM

After completing the baseline assessment, the nurse opened the sealed envelope that determined the families’ allocation group. The control group did not receive any information about avoidance measures; instead, they received the usual care provided by their primary care physicians. The intervention group received the following specific measures immediately after allocation at the end of the prenatal visit.

House Dust Mite Control Measures

All mattresses and box springs in the parents’ and the infants’ bedrooms were encased with vapor-impermeable covers. Parents were instructed to wash all bedding in hot water weekly. Research nurses applied benzyl benzoate powder (Acarosan powder; Bencard Laboratories–SmithKline Beecham Inc, Mississauga, Ontario) to carpets in these rooms and benzyl benzoate foam to the upholstered furniture in the most commonly used room before and at 4 and 8 months after birth. The powder was left on carpets for 8 to 12 hours before removal by vacuuming.

Pet Avoidance Measures

Parents who had cats, dogs, and other furry pets were counseled to remove them from the home. If this was not possible, they were instructed to keep pets outside the house and Winnipeg, Manitoba. Our intervention included measures to reduce exposure to house dust mite and pet allergens, avoidance of environmental tobacco smoke, encouragement of breastfeeding, and the use of a partially hydrolyzed formula. Results of the assessment of the infants at the age of 12 months are presented.

We describe a prospective, prenatally randomized, controlled study undertaken to determine the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants (in this study, infants are defined as persons from birth to the age of 1 year). The study was carried out in 2 centers in Canada: Vancouver, British Columbia,
or at least outside the infant’s bedroom. Parents without pets were advised not to get one.

**Smoke-Free Environment for the Infant**

Parents who were smokers were counseled on smoking cessation. Emphasis was placed on the necessity of abstinence from smoking by parents, other caregivers, and visitors inside the home and in the presence of the infant when outside the home.

**Breastfeeding and Dietary Avoidance**

Mothers were encouraged to breastfeed at least 4 months and for the first year if possible. When full breastfeeding was not possible, a partially hydrolyzed whey formula (Good Start; Nestle Canada Inc, North York, Ontario) was supplied to the infants for supplementation when necessary and after weaning, up to the age of 12 months. Infants who had allergic symptoms to the partially hydrolyzed formula were given soy formula. During the last trimester of pregnancy and during lactation, mothers were instructed to follow a diet excluding peanuts, other nuts, fish, and other seafood. Parents were counseled to delay the introduction of solids until the age of 6 months and were given a timetable of the types of food to be introduced after the age of 6 months. Parents were also advised to exclude cow’s milk, seafood, and peanuts from the infant’s diet during at least the first year of life.

The intervention families were also encouraged to avoid using day care facilities. During subsequent visits, the research nurse reinforced the various avoidance measures.

**OUTCOME ASSESSMENT AT 12 MONTHS**

At the end of 12 months, each infant was seen by 1 pediatric allergist at each center who was blinded to the randomization and to the families’ compliance with intervention measures and who did not provide health care services to the families. Allergy skin tests were done by research nurses using the epicutaneous method with a prick (Laneto the families. Allergy skin tests were done by research nurses using the epicutaneous method with a prick (Laneto the families. Allergy skin tests were done by research nurses using the epicutaneous method with a prick (Laneto the families.

**Ethics**

The study was approved by the ethics committees of the University of British Columbia, Vancouver, and the University of Manitoba, Winnipeg.

**Statistical Analyses**

The principal statistical analysis was the comparison of the intervention group with the control (usual care) group on the intent-to-intervene basis. We calculated the cumulative incidence (percentage) of the outcomes previously defined for both groups. The primary outcome was combined possible or probable asthma. Our hypothesis was that the multifaceted intervention program reduces the risk of possible or probable asthma. The risk reduction (percentage) was calculated as follows: (1 relative risk of being in the intervention group) × 100, using the odds ratio from the logistic regression model as an estimate of relative risk.

Because we hypothesized that the intervention program reduces the risk, we used a 1-sided test of significance for the hypothesis testing and estimated the appropriate 90% confidence interval.

We used t-test and $\chi^2$ statistics to compare the distribution of covariates (sex, ethnic origin, order of birth, city of birth, family history of asthma or other allergic disorders, and maternal educational level) at baseline between the control and the intervention groups. The data were normally distributed. An analysis of variance for repeated measurements was used to test for differences in house dust mite and cat allergen levels between the 2 groups at different points: prenatally and at 2 weeks and 4, 8, and 12 months after birth. Because the 2 groups differed for only 1 covariate (mother’s postsecondary educational level), we included this variable in the logistic regression model to control for the potential confounding effect of this variable.

Statistical analysis was carried out using personal computer software (Statistical Product and Service Solutions, version 4; SPSS Inc, Chicago, Ill) and statistical software (Stata, version 5.0 for Windows 95; Stata Corp, College Station, Tex).

**RESULTS**

**Characteristics of Study Families**

The intervention and the control groups were similar in sex, proportion of firstborn infants, and family history of asthma and allergic disorders (Table 1). There was no difference in the ethnic origin of the 2 groups, with approximately 80% whites in both groups; Asians made up about half of the nonwhites. A significantly lower proportion of mothers in the intervention group received postsecondary education than those in the control group. The characteristics of the homes, including age, type of dwelling, heating, fuel used, presence of dampness, leaks,
and water damage, were not different between the 2 groups (data not shown).

RESPONSE TO INTERVENTION MEASURES

There were no differences between the intervention and the control groups in the prevalence of smoking prenatally and at 12 months after birth (Table 2). Only 15 (6%) of the 251 mothers in the intervention group and 21 (8.7%) of the 242 mothers in the control group were smokers at the outset of the study. However, an additional 16 (6%) of the women in the intervention group and 21 (8.7%) of the women in the control group were smoking 1 year before enrollment but had already stopped smoking before the beginning of the study. During the 12-month study period, some smokers gave up smoking, while some nonsmokers initiated smoking. There were no differences in the proportion of mothers, fathers, and others who gave up smoking or acquired smoking habits between the 2 groups.

In the intervention group, only 9 (3.6%) of the parents did not use the mattress encasement provided for their beds, and 11 (4.4%) did not use the encasement provided for the infants’ beds. On average, 6.5% of the families in the intervention group did not have a benzyl benzoate application on the carpets. There were no differences between the intervention and the control groups in the levels of mite allergen in their homes prenatally (geometric mean, 1.31 vs 1.46 µg/g of dust) (Figure 2). Mite allergen levels were reduced by about one third in the intervention group at 12 months after birth, significantly different from those in the control group at all intervals. The reduction in mite allergen levels was primarily due to encasement of mattresses rather than to the application of benzyl benzoate to carpets.

There was also no difference in the prevalence of pet ownership prenatally and at 12 months after birth between the 2 groups (Table 2). At 12 months after birth, 17 (30%) of the 57 intervention families who had a cat initially gave up the pet compared with 11 (23%) of 48 control families; an equal proportion (1 [2%]) of families in both groups without a cat initially acquired a cat by the time the infant was aged 12 months. The differences between the 2 groups were not significant (P = .69). Cat allergen levels in homes of both groups were not different prenatally, and the levels declined significantly at 12 months in both groups (Figure 2). The average cat allergen levels in the intervention group were significantly lower at 2 weeks (P = .03) and 4 months (P = .04) after birth than those in the control group. In both groups, the levels were significantly lower in homes that gave up cats than in homes that kept them or acquired them. In homes without cats at all times, average cat allergen levels were lower in the intervention group than in the con-

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Study Groups*</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>ETHNIC ORIGIN</td>
</tr>
<tr>
<td>Whites</td>
</tr>
<tr>
<td>Asians</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>First born</td>
</tr>
<tr>
<td>FAMILY HISTORY</td>
</tr>
<tr>
<td>≥1 FDRs with asthma</td>
</tr>
<tr>
<td>≥2 FDRs with other allergies</td>
</tr>
<tr>
<td>MOTHER WITH ASTHMA</td>
</tr>
<tr>
<td>FATHER WITH ASTHMA</td>
</tr>
<tr>
<td>Mothers received postsecondary education</td>
</tr>
</tbody>
</table>

*Data are given as the number (percentage) in each group unless otherwise indicated. FDR indicates first-degree relative.
† Obtained by χ² analysis.
‡ There were 7 single mothers in the control group and 6 single mothers in the intervention group.

<table>
<thead>
<tr>
<th>Table 2. Prevalence of Smokers and Pet Owners Prenatally and at 12 Months After Birth*</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Smokers at 12 mo After Birth</td>
</tr>
<tr>
<td>Parent</td>
</tr>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Father</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Pet owners</td>
</tr>
<tr>
<td>Cat</td>
</tr>
<tr>
<td>Dog</td>
</tr>
<tr>
<td>Any</td>
</tr>
</tbody>
</table>

*Data are given as the number (percentage) in each group. Differences between groups are not statistically significant prenatally or at 12 months after birth for all variables.
control group at all times, and the differences were significant at 2 weeks ($P=.002$) and at 12 months ($P=.01$).

From birth, a high proportion of mothers in both groups breastfed their infants (93% and 92%, intervention and control groups, respectively). At 8 months after birth, differences between the intervention and the control groups were significant (61% vs 50%; $P=.02$) due to a higher percentage of intervention infants still being partially breastfed. Only 8.3% of control infants were given partially hydrolyzed formula, and 2.8% of infants in the intervention group were given cow’s milk at some time during the 12-month period. There was a significant delay in the introduction of solid food in the intervention group. Only 19.5% of the intervention infants received solids by the age of 4 months compared with 49.8% of the control infants ($P<.001$). Most infants were cared for at home. The proportion of infants cared for at day care facilities was significantly lower in the intervention group than in the control group at 8 (2.4% vs 7.4%; $P=.01$) and 12 (3.6% vs 10.3%; $P=.004$) months.

**RESPIRATORY TRACT OUTCOMES AND SKIN TEST RESULTS AT 12 MONTHS**

**Table 3** shows the incidence of outcomes at 12 months by treatment groups and the unadjusted and the adjusted (for differences in maternal educational level between the 2 treatment groups) relative risks. The risk for possible or probable asthma was significantly reduced in the intervention group by 34%.

Of the 87 infants who fulfilled the criteria for possible or probable asthma, 21 had at least 2 distinct episodes of wheeze, each lasting for 1 or more weeks, and at least 2 distinct episodes of cough, each lasting for 2 or more weeks; 23 had at least 2 distinct episodes of cough, each lasting for more than 2 weeks; 7 had at least 2 distinct episodes of wheeze, each lasting for more than 1 week (some of these infants also had additional symptoms); 10 had nocturnal cough (7 had additional chest symptoms) in the absence of a cold; 18 had hyperpnea-induced wheeze or cough in the absence of a cold; and the remaining 8 had a combination of chest symptoms with or without a response to treatment.

The risk for rhinitis without colds was significantly reduced in the intervention group by 49%. The incidence of a positive skin test reaction to inhalant was similar in the 2 treatment groups. In the intervention group, 9 infants reacted to cat and 2 to dog. In the control group, 4 infants reacted to cat, 1 to dog, 2 to cockroach, 1 to Cladosporium, 2 to Alternaria, and 1 to both D farinae and Alternaria. There was no correlation between a positive skin test reaction to cat and respiratory tract symptoms. There was no significant ($P=.56$) difference in the incidence of positive skin test results to food allergens.

Twelve (4.8%) of the infants in the intervention group and 17 (7%) of the infants in the control group had bronchiolitis (reported by parents) ($P=.30$). A significantly greater proportion of those with bronchiolitis in both groups was categorized as having possible or probable asthma compared with those without such a label, but no significant differences were found in the relation of bronchiolitis and possible or probable asthma between the 2 groups.

In this study, we demonstrated that the multifaceted intervention program in high-risk infants during the first 12 months of life resulted in a modest but significant reduction in the risk of possible or probable asthma by 34%; probable asthma, 46%; and rhinitis without colds, 49%.

It is difficult to make a diagnosis of asthma at the age of 12 months. Recurrent wheeze during the first year of life may not be associated with asthma in later years. Martinez and colleagues$^{19}$ have conducted a prospective study of 1240 newborns in Tuscon, Ariz. Of the 277 infants who had wheeze before the age of 3 years, 164 (59.2%) had no wheeze during the previous year when they were examined at the age of 6 years (transient wheezers); the rest had persistent wheeze. Because of this issue, rather than using the term asthma, we used possible and probable asthma based on strict criteria that were prospectively agreed on by the investigators. To satisfy the criteria of possible asthma, the infant must have had recurrent wheeze or recurrent cough or nocturnal or hyperpnea-induced cough or wheeze in the absence of a cold and these symptoms must be of certain duration or frequency, as stated in the “Outcome Assessment at 12
Table 3. Incidence of Respiratory Tract Outcome and Skin Test Reaction at 12 Months After Birth*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (n = 242)†</th>
<th>Intervention Group (n = 251)†</th>
<th>Crude RR (90% CI)</th>
<th>Adjusted RR (90% CI)‡</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>49 (20.2)</td>
<td>38 (15.1)</td>
<td>0.70 (0.47-1.04)</td>
<td>0.66 (0.44-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>Possible</td>
<td>28 (11.6)</td>
<td>24 (9.6)</td>
<td>0.81 (0.50-1.31)</td>
<td>0.80 (0.49-1.31)</td>
<td>.23</td>
</tr>
<tr>
<td>Probable</td>
<td>21 (8.7)</td>
<td>14 (5.6)</td>
<td>0.62 (0.35-1.12)</td>
<td>0.54 (0.29-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>Rhinitis without cold</td>
<td>66 (27.3)</td>
<td>42 (16.7)</td>
<td>0.54 (0.37-0.77)</td>
<td>0.51 (0.35-0.74)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Positive skin test result to an aeroallergen§</td>
<td>11 (4.6)</td>
<td>11 (4.4)</td>
<td>0.95 (0.47-1.94)</td>
<td>0.92 (0.45-1.90)</td>
<td>.43</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.
†Data are given as number (percentage) in each group.
‡Adjusted for maternal educational level (postsecondary vs no postsecondary education), using multiple logistical regression.
§Aeroallergens include house dust mites, cats, dogs, cockroaches, Alternaria, and Cladosporium.
behavior of the control group may have reduced the differences in findings between the 2 groups. A contributing factor to this contamination is the educational level of mothers in this study, which is above average: 82.2% of mothers in the control group had some postsecondary education, while the figures for the general population were 41.9% and 37.2% in Vancouver and Winnipeg, respectively. The high maternal educational level may explain the relatively low prevalence of smoking and the relatively high rate of breastfeeding in both groups.

In summary, the multifaceted intervention program instituted just before birth resulted in a modest but significant reduction in the relative risk of possible or probable asthma by 34% and rhinitis without colds by 49% at the age of 12 months in high-risk infants but failed to reduce the incidence of sensitization to inhalant allergens. The difference in the incidence of probable or possible asthma between groups is not due to differences in access to health care facilities since all families used the same and only health care plan in Canada. Because of the difficulties in making the diagnosis of asthma at the age of 12 months, follow-up study of this cohort is vital to determine the effectiveness of the intervention program in the primary prevention of asthma.

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From the Occupational and Environmental Lung Diseases Unit, Respiratory Division, Department of Medicine (Drs Chan-Yeung and Dimich-Ward), and the Division of Allergy, Department of Paediatrics (Dr Ferguson), University of British Columbia, Vancouver; and the Departments of Medicine and Community Health Sciences (Dr Manfreda) and the Section of Allergy and Clinical Immunology, Department of Paediatrics and Child Health (Drs Watson and Becker), University of Manitoba, Winnipeg. Dr Chan-Yeung is now with the University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, Special Administrative Region, China.

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Reprints: Moira Chan-Yeung, MB, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Room 418, Professorial Block, Hong Kong, Special Administrative Region, China.

REFERENCES

20. Profile of Census Tracts in Abbotsford and Vancouver. Ottawa, Ontario: Minis-