

PREDICTION, PREVENTION, AND THE "HYGIENE HYPOTHESIS"

THE CANADIAN ASTHMA PRIMARY PREVENTION STUDY: OUTCOMES AT 2 YEARS OF AGE

Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. *J Allergy Clin Immunol.* 2004;113:650–656

Purpose of the Study. To determine the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants.

Study Population. Subjects were children ($n = 549$) born between October 1994 and August 1996, classified as high-risk for development of asthma on the basis of family history.

Methods. A prospective, controlled clinical trial identified mothers in their third trimester of pregnancy and randomized each mother into either the multifaceted-intervention group ($n = 278$) or control group ($n = 267$). The intervention program was implemented during the first year of life and included decreasing allergen (dust mite and pet) and environmental tobacco-smoke exposure, encouraging breastfeeding, and delaying introduction of solid foods. The control group did not receive specific intervention education. Home visits conducted during the third trimester, at 2 weeks, and at 4, 8, 12, 18, and 24 months of age assessed health, demographic, and home characteristics, and dust samples were collected to quantify house dust-mite and cat-allergen levels. Infants in each group were evaluated and prick skin-tested for common food and environmental allergens at 12 months and 2 years of age. Study participants were assessed for possible asthma, probable asthma, recurrent wheeze, recurrent cough, rhinitis without colds, and atopy (defined as positive skin test to ≥ 1 allergen).

Results. In terms of intervention efficacy, there were significant differences in cat-allergen exposure (with no change in prevalence of pets) and day care enrollment between the groups. Asthma was characterized as the sum of possible and probable asthma diagnoses. At 2 years, 40 of 246 (16.3%) intervention children and 53 of 230 (23%) control children were classified as asthmatic. There was a significant reduction in persistent asthma (children meeting criteria for asthma at both 12 and 24 months of age), with only 4.9% of the intervention group versus 11.3% of the control group characterized as having persistent asthma. There was no difference between the groups in regard to recurrent cough and no difference in incidence in the first year of life of recurrent wheeze. However, at 2 years, there were significantly fewer children in the intervention group with recurrent wheeze (1%) versus the control group (3.5%). The prevalence of atopy at 2 years was not different between the intervention (15.6%) and control (13.7%) groups.

Conclusions. The multifaceted intervention program, which focused on decreasing exposure in the first year of life to aeroallergens, food allergens, and environmental tobacco smoke for children deemed to be at high risk for development of asthma, was successful in significantly reducing the incidence of asthma at 2 years of age.

Reviewers' Comments. This study demonstrates that, in infants at high risk for developing asthma, reduction in allergen exposure and environmental modifications in the first year of life can significantly affect disease development and progression. Public health programs targeting

these interventions may greatly impact the increasing prevalence and morbidity of childhood asthma.

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FAMILY HISTORY, DUST MITE EXPOSURE IN EARLY CHILDHOOD, AND RISK FOR PEDIATRIC ATOPY AND ASTHMA

Cole Johnson C, Ownby DR, Havstad SL, Peterson EL. *J Allergy Clin Immunol.* 2004;114:105–110

Purpose of the Study. A birth cohort of a group of patients with substantial environmental burden of house dust mite were evaluated to determine the risk of exposure related to development of allergic disease and asthma.

Study Population. The study population was a part of the Childhood Allergy Study of the Health Maintenance Organization in a geographically defined area. The children (835) were born at term between 1987 and 1989 and were then followed from birth.

Methods. The mother was interviewed during her pregnancy and then followed after birth until 6 to 7 years of age. The patients had dust collected from their bedrooms that was analyzed for major allergens from house dust mites. Prick skin tests, specific serum IgE measurement, and methacholine challenge were performed.

Results. The only positive association was for bronchial hyperresponsiveness for house d-e allergen levels of $>2 \mu\text{g/g}$ of dust (odds ratio [OR]: 0.62; $P < .05$) and $>10 \mu\text{g/g}$ of dust (OR: 0.53; $P < .065$). With a parental history of allergy and asthma, there was an association between a positive d-e skin test (OR: 2.09; $P < .076$) and a d-e allergen level of $>10 \mu\text{g/g}$. The inverse was true for children without a parental history. D-e exposure of $>10 \mu\text{g/g}$ was associated with a decreased risk for recurrent atopic asthma in children with a parental history of allergic disease but without increased risk if there was no parental history.

Conclusions. Parental history is an important independent variable in the relationship between early house dust exposure and development of atopy. Increased exposure in infancy is associated with a high risk of sensitization in the presence of positive parental history but is protective in children of parents without a history of atopic disease.

Reviewer's Comments. This is a very important study. It helps put into better perspective the "hygiene hypothesis." The strong genetic determination of allergic disease is reinforced. The concept is particularly important to understand to make appropriate observations from the literature and translate this to counseling regarding their child's expected clinical course.

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PERINATAL PREDICTORS OF ATOPIC DERMATITIS OCCURRING IN THE FIRST SIX MONTHS OF LIFE

Moore MM, Rifas-Shiman SL, Rich-Edwards JW, et al. *Pediatrics.* 2004;113:468–474

Purpose of the Study. To prospectively investigate perinatal predictors of atopic dermatitis during the first 6 months of life.

Study Population. Study subjects were 1005 urban and suburban mothers and their infants enrolled in Project Viva, based in the greater Boston, Massachusetts, area. The

main outcome measure was maternal report of a provider's diagnosis of eczema or atopic dermatitis in the first 6 months of life.

Methods. The authors used a prospective birth cohort study design and multiple logistic-regression models to assess the associations between potential predictors and incidence of atopic dermatitis.

Results. The incidence of atopic dermatitis in the first 6 months of life was 17.1%. The risk of atopic dermatitis was increased among infants born to black or Asian mothers (adjusted odds ratio [OR]: 2.41 and 2.58, respectively) and among infants whose mothers had eczema (OR: 2.67). Other predictors included increased gestational age at birth (OR: 1.14; 95% confidence interval: 1.02, 1.27, for each 1-week increment) and male gender (OR: 1.76).

Conclusions. These findings suggest that genetic and prenatal and perinatal influences are important in the early presentation of atopic dermatitis.

Reviewer's Comments. There are relatively little data about risk factors for atopic dermatitis in the United States, and the strengths of this study are the prospective evaluation of risk factors in a large population with data collection beginning in the prenatal period. The results of the study point to a number of risk factors related to heredity and potentially genetics as being important in early onset of eczema. The preponderance of affected males is interesting given that infant boys are also more likely to wheeze. Although this may be due in part to changes in airway mechanics, the results of this study, together with data demonstrating higher total serum IgE levels in boys, suggest that immune development is also related to gender. Environmental factors were not prominent as risk factors for eczema, although there was a trend toward an association with greater cockroach exposure. It is likely that environmental exposures play a greater role in determining the persistence of atopic dermatitis or perhaps the incidence after the first 6 months of age.

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REDUCED INTERFERON γ PRODUCTION AND SOLUBLE CD14 LEVELS IN EARLY LIFE PREDICT RECURRENT WHEEZING BY 1 YEAR OF AGE

Guerra S, Lohman IC, Halonen M, Martinez FD, Wright AL. *Am J Respir Crit Care Med.* 2004;169:70–76

Purpose of the Study. To determine if interferon γ (IFN γ) production and soluble CD14 (sCD14) levels correlate longitudinally with the risk of developing recurrent wheezing in the first year of life. Both environmental risk factors and variation in the maturation of the immune system seem to have a role in the development of asthma. Previous studies have demonstrated reduced IFN γ production in atopic and nonatopic wheezers. IFN γ production correlates positively with endotoxin exposure and with sCD14 levels, and CD14 functions as a receptor for endotoxin. Thus, the investigators reasoned that a CD14-mediated response to endotoxin might play a role in the maturation of IFN γ production, possibly preventing the onset of recurrent wheezing.

Study Population. Subjects were 238 infants followed prospectively from birth to 12 months as part of the Infant Immune Study in Arizona.

Methods. Mothers of enrolled infants completed questionnaires about known environmental risk factors for wheezing before birth and throughout the infant's first 12 months of life. At 12 months, the mothers were also asked how often their infant's chest had ever sounded "wheezy"

or "whistling" and the age of the first wheezing episode. Frequency of wheezing was quantified, and any response more than "very rarely" was classified as recurrent wheezing. Blood was obtained at birth and 3 months of age for the measurement of sCD14 levels in plasma and IFN γ production from stimulated peripheral blood mononuclear cells.

Results. Wheezing episodes during the first year of life were experienced by 94 infants (39.5%), and 41 experienced recurrent episodes. The mean IFN γ production and sCD14 levels increased from birth to 3 months. Infants in the lowest quartile of IFN γ production at 3 months and of sCD14 levels at birth had up to 4.5 and 3.2 increased odds, respectively, of developing recurrent wheezing compared with children in the medium and high quartiles for these parameters. These relationships persisted after adjusting for demographic and environmental asthma risk factors.

Conclusions. The authors concluded that reduced plasma sCD14 at birth and impaired IFN γ production at 3 months of age increase the risk of recurrent wheezing in the first year of life. Because of the interrelationship of CD14 and IFN γ , a CD14-mediated response to endotoxin may play an important role in enhancing the maturation of IFN γ production and preventing the inception of recurrent wheezing.

Reviewers' Comments. The relation of CD14 and IFN with endotoxin exposure lends support for the "hygiene hypothesis," which postulates that decreased exposure to infectious agents in infancy increases the risk for atopy. From this study, it is impossible to assess whether sCD14 levels at birth and IFN γ production at 3 months of age are simply independent markers that correlate with recurrent wheeze or whether they are truly in the same causal pathway to recurrent wheezing. Additional studies will need to be done to confirm causality. Unfortunately, the design of the study did not allow the investigators to explore whether IFN γ production and sCD14 levels were important in atopic versus nonatopic recurrent wheezing.

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SOLUBLE CD14 AS A PREDICTOR OF SUBSEQUENT DEVELOPMENT OF RECURRENT WHEEZING IN HOSPITALIZED YOUNG CHILDREN WITH RESPIRATORY SYNCYTIAL VIRUS-INDUCED BRONCHIOLITIS

Soferman R, Bar-Zohar D, Jurgenson U, Fireman E. *Ann Allergy Asthma Immunol.* 2004;92:545–548

Purpose of the Study. To investigate the relationship between the serum level of soluble CD14 (sCD14) in children hospitalized because of respiratory syncytial virus (RSV)-induced bronchiolitis and the subsequent development of recurrent wheezing.

Study Population. Twenty-one infants aged 2 to 14 months who were hospitalized because of RSV bronchiolitis in the winter of 2001–2002. All were at least 37 weeks' gestation without any neonatal complications or prior illness.

Methods. sCD14 was measured on admission to the hospital. RSV infection was documented by direct immunofluorescence. Children were assessed every 2 months for 1 year after discharge for the development of recurrent wheezing.

Results. Nineteen patients completed the study. Six children did not have recurrent wheezing in the 12-month

Perinatal Predictors of Atopic Dermatitis Occurring in the First Six Months of Life

James E. Gern

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