

Environmental factors influencing the development and progression of pediatric asthma

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Recent data underscore the importance of environmental factors in the sensitization of children to certain allergens and the development of asthma. Maternal smoking and family (especially maternal) history of atopy appear to be risk factors for persistent sensitization and development of asthma. Indeed, exposure to tobacco smoke in utero significantly increases asthma risk and influences the timing of sensitization. It must be stated that any smoking at home has consequences for the development of asthma and other respiratory conditions. In addition, reports of possible protective effects of specific environmental conditions suggest that exposure to certain stimuli may reduce or block the development and progression of asthma. Attendance at a day care center early in life appears to offer protective effects against wheezing, as do early episodes of rhinitis, herpes, and measles. Children raised on a farm also have a decreased prevalence of atopic diseases. The protective effect of contact with livestock and poultry is consistent among several studies. Although the pathophysiologic mechanisms involved remain undefined, studies suggest that exposure to endotoxin and other components of bacteria may play an important role in protecting against childhood atopic diseases. Whether in utero exposure is beneficial remains to be determined. (*J Allergy Clin Immunol* 2002;109:S525-32.)

Key words: Asthma, atopy, environmental factors, risk factors, sensitization

Much remains obscure about the pathogenesis and natural history of asthma. However, recent data confirm the importance of several factors in the development of asthma and suggest new mechanisms of asthma pathology. Longitudinal studies have shown that even when not diagnosed until adulthood, asthma often begins in early life, with wheezing symptoms. Adults with asthma often think their disease began during early adulthood, but when they review their childhood medical records, most find that their wheezing episodes actually began quite early in life. The results of a community-based study of this question are shown in Figure 1.¹ As shown in the figure, incidence rates for definite and probable asthma combined were highest in infants younger than 1 year of

Abbreviations used

BHR: Bronchial hyperresponsiveness
LRI: Lower respiratory tract infection
OR: Odds ratio
RR: Relative risk

age (boys > girls); rates declined progressively throughout childhood and were lowest in adults.

RISK FACTORS FOR ASTHMA Atopic sensitization and asthma

The German multicenter allergy study² (MAS) followed 1314 children from birth to 7 years of age; 499 of these children were at risk for atopy (elevated cord blood IgE, at least 2 family members with atopy, or both). All children had their serum IgE levels to food and inhalant allergens measured at each birthday, except for age 4 years. This population was classified into 4 groups: (1) children who were never sensitized at any time during the first 7 years, (2) children with transient early sensitization who had early sensitization to any allergen and no late sensitization to inhalant allergens, (3) children with late-onset sensitization to inhalant allergens who had no early sensitization to any allergens, and (4) children with persistent sensitization who had both early sensitization to any allergens and late sensitization to inhalant allergens.

At the 7th-year visit, 939 (71.5%) children participated in the follow-up studies. At age 7, these children were also classified into the following groups: (1) "currently wheezing" if the parents reported at least 1 episode of wheezing in the prior 12 months, (2) "diagnosis of asthma ever" if the child ever had a physician's diagnosis of asthma, (3) "current asthma" if the child was diagnosed as asthmatic and a wheezer at age 7 years; (4) "current BHR" if the child had bronchial hyperresponsiveness (BHR) to histamine (645 [68.7%] children were tested for BHR).

Children who had asthma at age 7 years were sensitized very early in life and had a persistent sensitization compared with children who did not have asthma at age 7 years. The largest disparity between the asthma and the nonasthma groups for the time at which they were first measured for sensitization was found at age 1 year, when the children with asthma were twice as likely as the children without asthma to have been sensitized (~40% vs ~20%, respectively) (Fig 2).² The observed pattern, similar to that previously reported,³ was that asthmatic chil-

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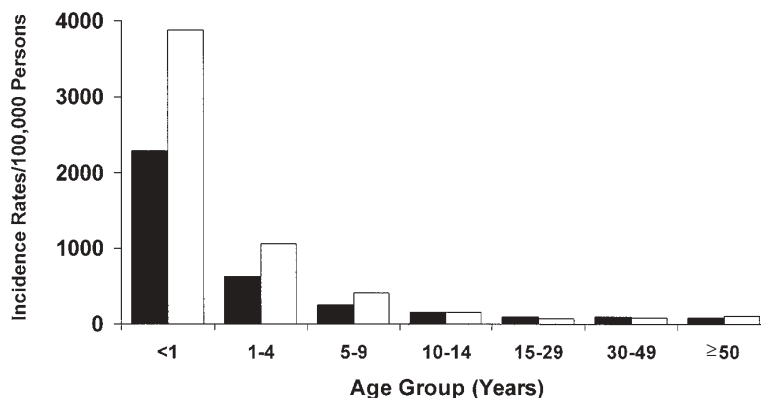


FIG 1. Annual incidence rates of definite and probable asthma. Among residents of Rochester, Minnesota, from 1964 to 1983, adults with asthma thought their disease began at age 20 years or during early adulthood, but a review of their medical records indicated that in most cases, the wheezing episodes actually began during their first 4 years of life. Unfilled bars are male subjects; filled bars, female subjects. (From Yunginger JW, Reed CE, O'Connell EJ, et al. A community-based study of the epidemiology of asthma: incidence rates, 1964-1983. *Am Rev Respir Dis* 1992;146:888-94. Official Journal of the American Thoracic Society. © American Lung Association.)

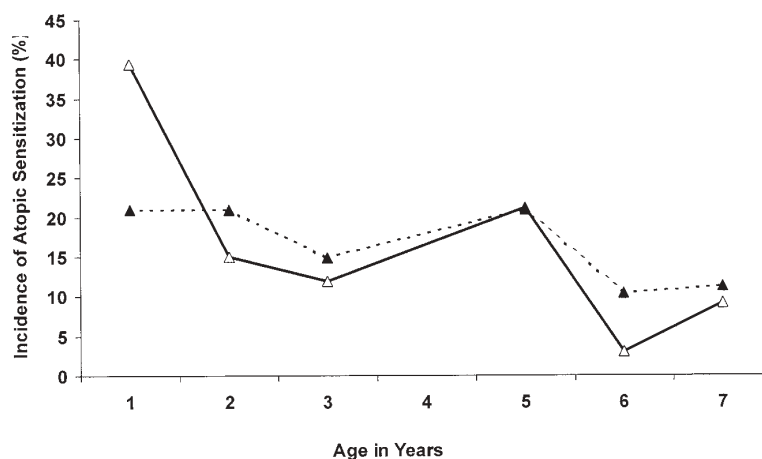


FIG 2. Age at onset of atopic sensitization in atopic children, stratified for current asthma at the age of 7 years. Children with asthma were twice as likely to have been sensitized at age 1 year as were children without asthma. Open triangles, asthmatic atopic subjects; filled triangles, nonasthmatic atopic subjects. (From Illi S, von Mutius E, Lau S, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001;108:709-14. With permission.)

dren were sensitized to any allergen during their first year and became sensitized to inhalant allergens later. In the German cohort,² transient sensitization did not increase the prevalence for asthma at age 7. Only persistently sensitized children had a significantly increased risk of being asthmatic at age 7 (odds ratio [OR], 10.12; 95% CI, 3.81 to 26.88 compared with never being sensitized). The development of asthma in children who had persistent sensitization may be associated with a specific phenotype; identifying the risk factors associated with this form of atopy may provide important information about the asthma that develops in these children.

Persistent versus transient sensitization

Several risk factors differentiated children with early sensitization who then had persistent sensitization from children with only transient sensitization. Among the risk factors for development of persistent sensitization is a family history of atopy or asthma (OR, 3.24; 95% CI, 1.75 to 6.00), with greater risk from the maternal history of atopy than from the paternal history (maternal atopy: OR, 4.50; 95% CI, 2.01 to 10.07; paternal atopy: OR, 1.36; 95% CI, 0.62 to 2.97). Without a family history of atopy or asthma, a persistent pattern of atopic sensitiza-

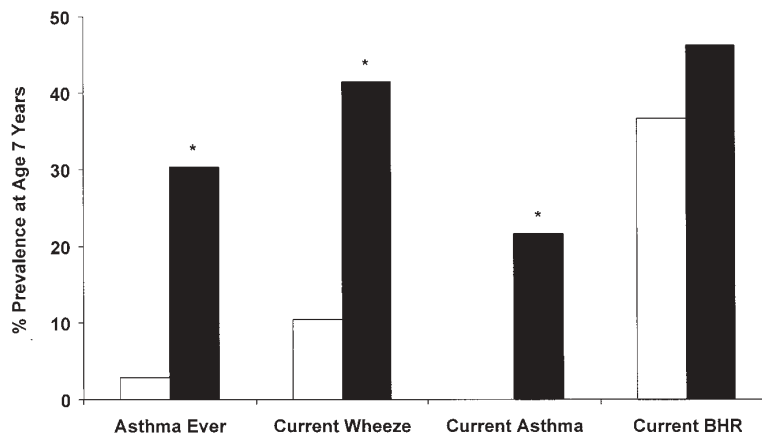


FIG 3. Prevalence of asthma and asthmatic symptoms at the age of 7 years in children with early and late sensitization (persistent sensitization), stratified for atopic family history. Unfilled bars, no family history of atopy or asthma; filled bars, positive family history of asthma. * $P < .01$. (From Illi S, von Mutius E, Lau S, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001;108:709-14. With permission.)

tion did not increase the risk for asthma at 7 years of age (Fig 3). Only persistently sensitized children who had a positive parental history of asthma or atopy were at significantly increased risk of being asthmatic at the age of 7 years (OR, 15.56; 95% CI, 5.78 to 41.83, compared with never being sensitized).² Therefore, sensitization alone does not cause asthma; rather, the underlying factors related to the positive family history for atopy appear to be responsible for the development of asthma and atopy.

In this German cohort, exposure to tobacco smoke in utero was another important risk factor for persistent sensitization and asthma. Maternal smoking during pregnancy significantly increased the risk for persistent sensitization (OR, 2.27; 95% CI, 1.14 to 4.52) and the risk for asthma at school age (OR, 2.46; 95% CI, 1.28 to 4.73). Furthermore, maternal smoking during pregnancy influenced the timing of sensitization. Children exposed to tobacco smoke in utero had an earlier onset of sensitization ($P = .04$) as compared with nonexposed children (data unpublished). These results are consistent with those of other studies of the relation between tobacco smoke and childhood asthma.⁴⁻⁶ Therefore, although the mechanisms that link a maternal history of atopy with asthma in children are unknown, both the genetic predisposition and environmental factors such as tobacco smoke have important synergistic effects in utero.

In the Tucson Children's Study,⁴ children of mothers who smoked half a pack of cigarettes or more per day (reported at the time of their child's enrollment; 75% of this smoking occurred at ≤ 2 years of age for the child) had a significantly higher relative risk (RR) of development of asthma (RR for boys, 1.63; RR for girls, 1.78; $P < .05$) than children whose mothers either smoked less than half a pack of cigarettes per day or did not smoke at all (Fig 4). However, there was no higher RR for asthma in children whose fathers smoked half a pack of cigarettes or more per day at the time of enrollment. Although maternal smoking during pregnancy was not

measured, the effects in children of mothers who smoked and not of fathers who smoked supports the idea that the elevated risk from smoking is great during pregnancy.

In a large British longitudinal study⁶ conducted in subjects from birth to 33 years of age, data were obtained from participants at 7, 11, 16, 23, and 33 years of age. At 7 years of age, 18% (1046 of 5801) of participants had a history of wheezing. The mother's smoking during pregnancy was an independent predictor of adult-onset wheezing. The OR associated with asthma or wheezing between 0 and 7 years of age for maternal smoking during pregnancy only versus no maternal smoking was 1.72. From age 8 through age 16, the OR decreased to 0.94, but from age 17 to age 33, it increased again (OR = 1.71). The children of mothers who smoked during pregnancy until the child's 16th birthday had a steadily increasing risk for wheezing compared with children whose mothers never smoked (OR at 0 to 7 years, 0.94; OR at 8 to 16 years, 1.10; OR at 17 to 33 years, 1.40). Clearly, maternal smoking is a risk factor for wheezing until the child is 7 years of age, and active smoking is a powerful risk factor for adult-onset wheezing.

In a recent meta-analysis⁵ assessing respiratory disease in children of mothers who smoked, the children (0 to 2 years of age) had an increased risk for wheeze, lower respiratory tract infection (LRI), and hospitalization for LRI (OR, 2.08, 1.72, and 1.53, respectively). At 5 to 16 years of age (that is, school age), the risks for wheeze, cough, and asthma were also higher for these children than for children whose mothers did not smoke (OR, 1.28, 1.40, and 1.36, respectively). When both parents smoked, the risk in school-age children for wheeze, cough, and asthma rose further (OR, 1.47, 1.67, and 1.50, respectively). The risks were higher in pre-school-age children than in school-age children, and they were higher for maternal smoking than for paternal smoking. However, for LRI in infancy and for wheeze and cough in school-age children, the effect of paternal smoking in households in which the

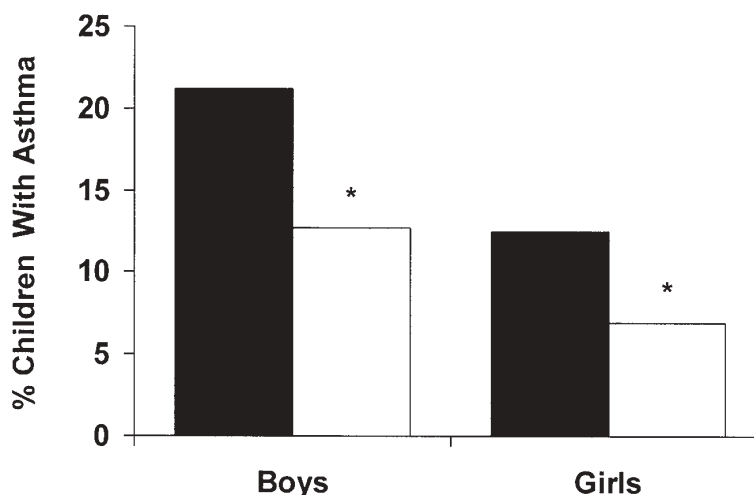


FIG 4. Relation between mother smoking at enrollment and subsequent development of asthma in their children. Children whose mothers smoked at least half a pack of cigarettes daily (solid bars) are at increased risk ($P < .05$) for asthma compared with children whose mothers smoked no cigarettes or less than half a pack daily (open bars). (Adapted from data in Martinez et al.⁴)

mother did not smoke was significant, underlining the consequences of any smoking at home for the development of asthma and other respiratory conditions.

Sensitization to inhalant allergens

In the German cohort,⁷ asthma was often associated with immediate hypersensitivity to indoor allergens, notably hypersensitivity derived from the house dust mite. A dose-response relation existed between the amount of allergen measured in carpet dust and sensitization at ages 1, 2, and 3 years. Children sensitized at least once in their first 3 years of life were found to have been exposed to significantly higher levels of dust mite allergen ($P = .001$) compared with children who had not been sensitized. In homes with low dust mite concentrations (in the lowest quartile of the concentrations measured), the risk of sensitization to dust mite was a low 1.6% compared with a 6.5% risk if the exposure was in the highest quartile.⁷ Similarly, a significant ($P < .001$) association between sensitization to house dust mite and wheezing was identified in children at 3 to 7 years of age, but no consistent dose-response relation existed between indoor allergen levels and a diagnosis of asthma, wheezing within the prior 12 months, or airway hyperresponsiveness.⁸ Although exposure to indoor allergens is associated with atopic sensitization to the specific allergen, a link with asthma was not seen. The strong relation between sensitization to house dust mites and asthma may therefore reflect the asthmatic individual's susceptibility to becoming sensitized to perennial allergens most prevalent in the environment rather than the elevated exposure to allergens being the direct cause of the increased risk of asthma. If this is so, and if the predisposition to becoming sensitized drives the development of asthma and not the elevated exposure to the allergen, factors other than exposure to indoor allergen may contribute to the development of asthma.

Further support for this notion comes from a study⁹ in Los Alamos, New Mexico, a high-altitude desert area and an environment in which there are very few house dust mites. Children growing up in this environment had a significantly lower cumulative prevalence of atopic sensitization to house dust mites than did children who were born elsewhere and who moved to the community ($P < .025$). Nevertheless, the prevalence of asthma remained high among the children born and raised in the Los Alamos community, with nearly 17% diagnosed as having asthma at some time and 14% taking asthma medication.⁹ Thus, although the prevalence of house dust mite sensitization is reduced in such areas, the prevalence of asthma is not.^{9,10}

PROTECTIVE FACTORS AGAINST ASTHMA

Early day care attendance and asthma

A 1992 study of East German children (5 to 14 years of age) who had been placed in a day care nursery in their preschool years examined the prevalence of asthma, hay fever, a positive skin prick test, and a positive RAST (radioallergosorbent test).¹¹ The prevalence was analyzed according to the time at which the child first entered preschool. Of children from small families (ie, fewer than 4 people living together) who entered day care, the later the child entered day care, the greater the prevalence of the respective atopic indicator (Fig 5). Using as a reference the children who entered preschool at age 6 to 11 months, a regression analysis showed a trend of increasing hay fever and positive skin prick test ($P < .01$) as children entered day care later. The number of children with asthma was too small to attain significance; the positive RAST tended toward significance. Inversely stated, the earlier children entered day care, the less the likelihood of developing atopy. A similar analysis of the children from large families showed no such association.¹¹

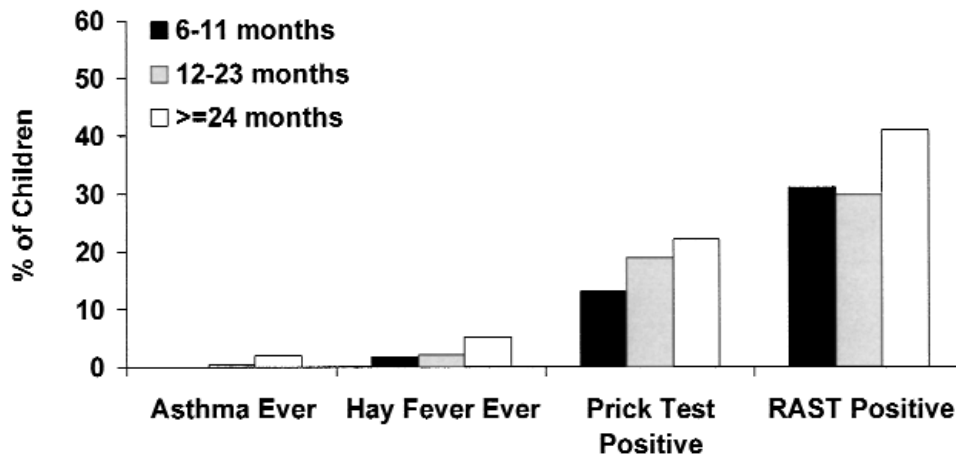


FIG 5. Percentage of children, 5 to 14 years of age, from small families (<4 members living together) with allergies, by age of entry to day nursery. Children who entered the day nursery at the youngest age had the fewest allergies (6 to 11 months); children who entered the day nursery at 2 years of age or older had the most allergies. (Adapted from data in Kramer et al.¹¹)

A more recent study¹² reported the protective effect against asthma in children who attended day care at an early age was reported. In 1035 children followed from birth, the incidence of asthma (defined as 1 episode of asthma diagnosed by a physician in children 6 to 13 years of age) and the prevalence of frequent wheezing (more than 3 wheezing episodes during the previous year) were compared with the corresponding incidence and prevalence in children who did or did not have older siblings and who did or did not attend day care. Children who attended day care during the first 6 months of life or who had older siblings were less likely to have asthma than were children who did not attend day care early in life. In children 2 years of age, the prevalence of frequent wheezing was significantly higher among those with greater exposure to other children (at home or in day care) than among those with less exposure (24% vs 17%, $P = .02$), but in children 11 and 13 years of age, the prevalence of frequent wheezing was significantly lower in the group with greater exposure (6% vs 11%, $P = .02$, and 5% vs 10%, $P = .04$, respectively). These results demonstrate that the development of asthma was less common among children with more exposure to other children at home or in day care during the first 6 months of life than among children with little or no such exposure.¹²

Early episodes of rhinitis and asthma

Episodes of rhinitis early in life may also protect against the development of asthma. In the German cohort, BHR and the prevalence of wheeze were followed for 7 years in children who had had at least 2 episodes of rhinitis in the first year of life compared with children who had had no more than 1 episode of rhinitis in the first year of life (reference population).¹³ Recurrent episodes of rhinitis (at least 2 in the first year) reduced the ORs for asthma diagnosis and wheeze to 0.52 and 0.60, respectively, for children at age 7 years. Similar protective effects were noted with repeated viral infections other than LRIs early in life (eg, with herpes virus).¹³

Prevalence of atopic diseases in farm children

Several studies have examined the possible protective effects of a farming environment against asthma in children. In a large cohort of Bavarian children ($n = 9647$) living in 2 rural districts, either on a farm or in a rural, nonfarming setting, the prevalence of hay fever, runny nose, asthma, and wheeze during the prior 12 months was significantly decreased ($P < .05$) in children living on a farm (Fig 6).¹⁴ Similar results were obtained in a study from Austria¹⁵; wheezy bronchitis, current wheeze, and atopy (skin prick test) were significantly reduced (18.8% vs 32.7%, $P = .001$). In addition, children from Swiss farming families were at significantly lower risk for having a positive RAST (SX₁) (OR, 0.31; 95% CI, 0.13 to 0.73) and for having specific IgEs to outdoor (OR, 0.38; 95% CI, 0.16 to 0.87) and indoor (OR, 0.15; 95% CI, 0.04 to 0.57) allergens than were children from nonfarming families.¹⁶

What factors are linked to the apparent protective effects of a farm environment, and how can they be identified? With the use of a stepwise approach and a multivariate logistic regression model, potential explanatory variables were entered into a multivariable statistical model. If the risk estimate did not change when a variable was added, that particular variable did not explain much of the "farming effect." In the Austrian study, the OR for allergic sensitization (skin test reactivity) associated with the crude effects of farming was 0.48 for children living on a farm versus children living in a nonfarming environment (Table I). When family history, maternal education, number of siblings, and housing conditions such as dampness or exposure to cigarette smoke were included in the model, the OR remained unchanged. The inclusion of infection during early years and diet raised the OR only to 0.51, as did regular contact with pets (OR, 0.54); these increases were not sig-

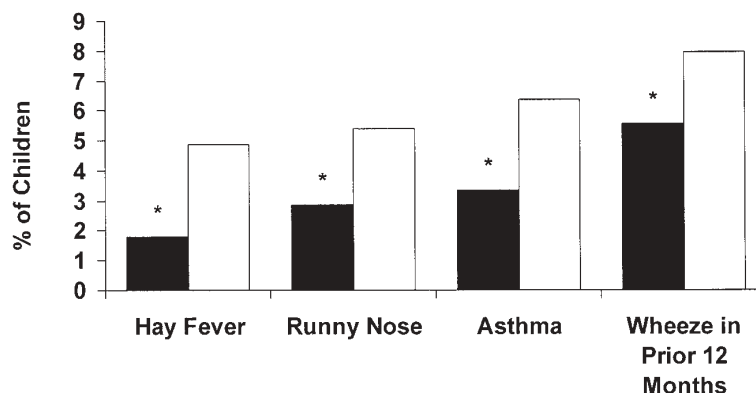


FIG 6. Prevalence of atopic diseases in children of farming (filled bars) and nonfarming parents (unfilled bars). Children living on a farm had a significantly lower risk (%) for atopic diseases than children from non-farming families, suggesting a protective effect of the farming environment against the development of atopic diseases. * $P < .05$. (Adapted from data in von Ehrenstein et al.¹⁴)

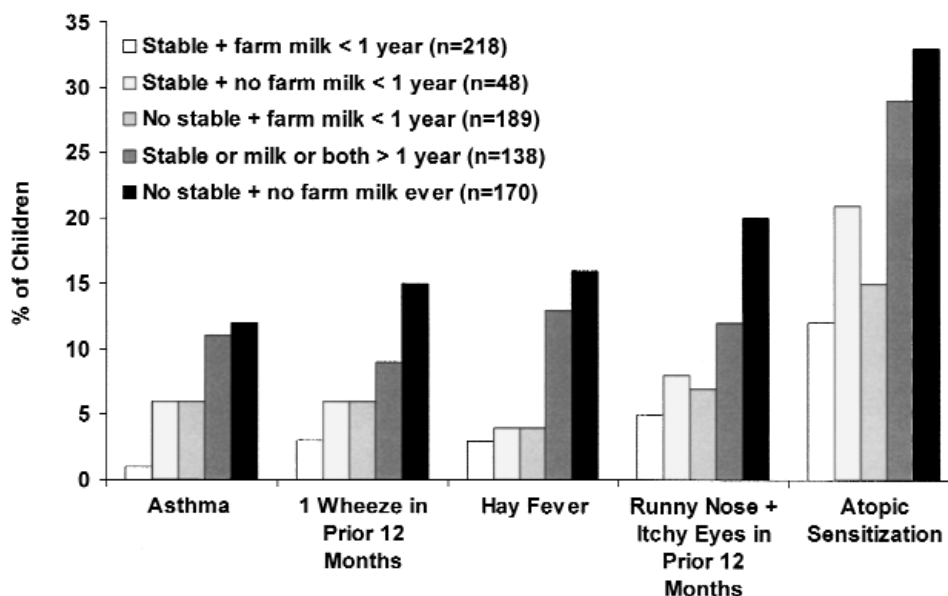


FIG 7. Frequency of asthma hay fever and atopic sensitization in relation to exposure to stable and farm milk in the first year of life. (Adapted from data in Riedler et al.¹⁷)

nificant. When regular contact with livestock and poultry was added to the model, the OR significantly changed to 0.75, indicating an important association between regular contact with livestock and reduced risk of atopic sensitization. Both the German and the Swiss studies yielded similar results. The importance of exposure to livestock was further emphasized in a study of children who did not live on a farm but who had regular contact with livestock through their peers and friends of these children who did have such contact. The children with regular contact with livestock also had a lower prevalence of allergic sensitization (13.5% vs 34.8%, $P = .01$).¹⁵

The effect of contact with livestock and poultry is consistent among several studies.¹⁴⁻¹⁶ Notably, in the Bavari-

an study, in which 88% of the farmers kept livestock, the risk of development of atopic disease among the farmers' children was significantly lower: The prevalence of atopic disease was 13.6% ($P < .005$), and the OR was 0.41.¹⁴ A multinational study (German, Austria, and Switzerland) examined the effects of the farming environment and confirmed the results of other studies that had shown that the prevalence of asthma, wheezing, hay fever, and runny nose/itchy eyes during the previous 12 months was lower among children living on a farm than among children not living on a farm.¹⁷ The risk for development of asthma and hay fever symptoms was significantly lower in farm children than in children from nonfarming environments (adjusted ORs, 0.30; 95% CI, 0.15 to 0.61, and 0.43, 0.24

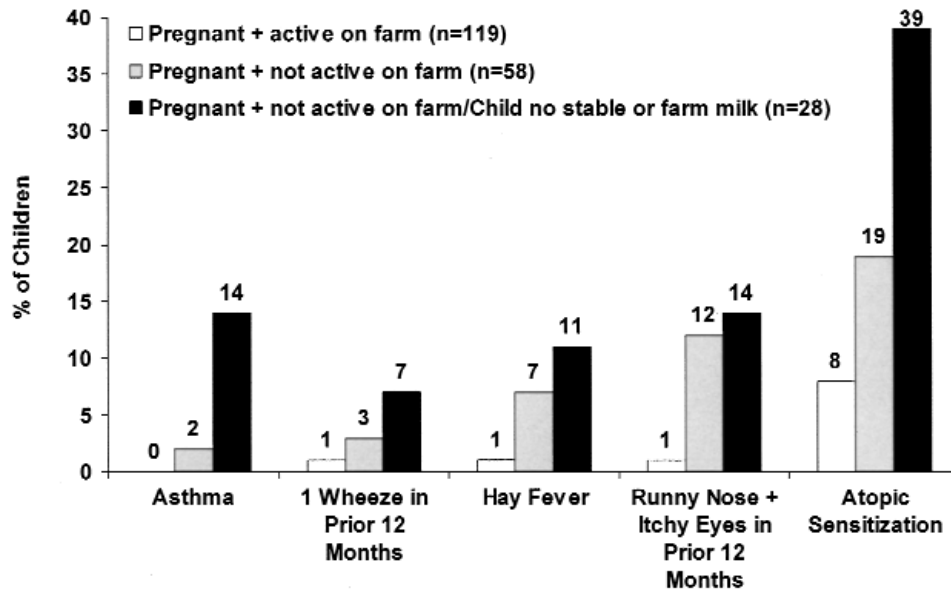


FIG 8. Frequency of asthma, hay fever, and atopic sensitization in farmers' children exposed to stables and farm milk in their first year of life in relation to the farming activity of their mothers during pregnancy. (Adapted from data in Riedler et al.¹⁷)

TABLE I. Changes in odds ratio at the various stages of the multivariate logistic regression model for the association of living on a farm and allergic sensitization

Table available in print only

to 0.77, respectively). However, exposure to a farm environment is not restricted to farmer's children.

Children exposed to stables and/or farm milk during their first year showed substantial protection against the development of asthma, hay fever, and allergic sensitization (Fig 7). These protective factors appeared to have additive effects; the lowest frequencies of diseases were found in children who had been exposed to both stables and farm milk in their first year of life. Exposure after the first year conferred no significant protection compared with unexposed children. Because this protection appeared to be conferred very early in life (in the first year), this raised the question of whether this protection might be started even earlier. In this study, two thirds of mothers of infants who were exposed to stables in their first year were active on the farm every day of their pregnancy. Prenatal exposure had a substantial protective effect (Fig 8). Therefore, exposure to the farm environment has a protective effect against asthma, hay fever, and atopic sensitization. Furthermore, the timing of the exposure, in utero or during the first year of life, is crucial.

Protective factors: A hypothesis

The pathophysiologic mechanisms associated with a farm environment that produce a protective effect remain undefined. A child's exposure to increased concentrations of bacterial components that are present in stables, such as endotoxin, may stimulate an immune system response.¹⁸ Samples of settled and airborne dust were collected in stables, and settled dust was collected from kitchen floors and children's mattresses in the houses of both farming and nonfarming families. Endotoxin concentrations were highest in the stables of farming families; endotoxin concentrations were significantly ($P < .001$) higher indoors in dust collected from the kitchen floor and the children's mattresses compared with the dust collected from the houses of nonfarming families. Endotoxin concentrations were also greater in dust collected from mattresses and kitchen floors in the homes of children who had regular contact with farm animals compared with the concentrations found in the homes of children who had no such contact. These findings suggest

that exposure to endotoxin and other bacterial components may play an important protective role against childhood atopic diseases.¹⁸

In a follow-up study¹⁹ of individuals living in areas with a lower prevalence of asthma and atopy (urban homes and farm homes and associated barns in the United States, homes in rural India and Peru inhabited by similar animals), the concentrations of endotoxin were significantly higher in rural and farm homes than in urban homes ($P < .001$). The barns contained the highest endotoxin concentrations, and endotoxin levels in farm homes and barns correlated significantly (Spearman $r = 0.67$; $P = .02$). Thus, the link between higher levels of endotoxin and areas of low prevalence of asthma and atopy strongly suggests that environmental exposure to endotoxin may offer protection against allergy and asthma. Whether there is an atopy-reducing benefit to the child in utero when its mother is in such an environment remains to be determined.

Endotoxins interact with the immune response to decrease sensitization in the following way: When a subject is exposed to a high burden of microbes, such as gram-positive, gram-negative, or atypical microbacteria, the microbes combine with dendritic cells through particular receptors that cause the production of IL-12, a very strong inducer of the T_H1 response. This IL-12-driven response leads away from the development of the T_H2 response and atopic sensitization.¹⁸

CONCLUSIONS

The first symptoms of asthma often appear early in life, with a high incidence of first symptoms in children younger than 4 years of age. Identifying risk factors for persistent sensitization and subsequent development of wheezing has significant implications for both prevention and long-term treatment of asthma. A family history of atopy, especially a history of maternal atopy, appears to lead to a predisposed response to allergens, resulting in asthma and atopy. Exposure to certain substances in utero, such as with maternal smoking during pregnancy, subjects the developing child to a primary risk factor for airway disease. Early and persistent sensitization are known risk factors for asthma, and sensitization to common aeroallergens such as dust mite especially increases the risk for wheezing. In contrast, early-life exposure to endotoxins when living on a farm may reduce the risk of sensitization and asthma. The precise mechanisms remain to be defined, but endotoxin exposure may induce a shift from T_H2 -type immunity to T_H1 -type responses. Whether exposure of a child in utero to endotoxin is beneficial remains to be determined. Defining the intricacies of allergen-specific responses in children could provide ways to prevent the development of asthma and atopy and improve long-term asthma treatment.

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