SIBLINGS, DAY-CARE ATTENDANCE, AND THE RISK OF ASTHMA AND WHEEZING DURING CHILDHOOD

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ABSTRACT

Background Young children with older siblings and those who attend day care are at increased risk for infections, which in turn may protect against the development of allergic diseases, including asthma. However, the results of studies examining the relation between exposure to other children and the subsequent development of asthma have been conflicting.

Methods In a study involving 1035 children followed since birth as part of the Tucson Children's Respiratory Study, we determined the incidence of asthma (defined as at least one episode of asthma diagnosed by a physician when the child was 6 to 13 years old) and the prevalence of frequent wheezing (more than three wheezing episodes during the preceding year) in relation to the number of siblings at home and in relation to attendance at day care during infancy.

Results The presence of one or more older siblings at home protected against the development of asthma (adjusted relative risk for each additional older sibling, 0.8; 95 percent confidence interval, 0.7 to 1.0; P=0.04), as did attendance at day care during the first six months of life (adjusted relative risk, 0.4; 95 percent confidence interval, 0.2 to 1.0; P=0.04). Children with more exposure to other children at home or at day care were more likely to have frequent wheezing at the age of 2 years than children with little or no exposure (adjusted relative risk, 1.4; 95 percent confidence interval, 1.1 to 1.8; P=0.01) but were less likely to have frequent wheezing from the age of 6 (adjusted relative risk, 0.8; 95 percent confidence interval, 0.6 to 1.0; P=0.03) through the age of 13 (adjusted relative risk, 0.3; 95 percent confidence interval, 0.2 to 0.5; P<0.001).

Conclusions Exposure of young children to older children at home or to other children at day care protects against the development of asthma and frequent wheezing later in childhood. (N Engl J Med 2000;343:538-43.)

BOTH the incidence and the prevalence of asthma among children have increased dramatically in the past three decades,[1,2] making it the most common chronic disease of childhood in the United States.[3] Although the cause of this epidemic remains unclear, one hypothesis is that a decrease in infections during early childhood may be partly responsible.[4] In support of this hypothesis, the frequency of several allergic disorders has been found to be inversely associated not only with childhood infections[5-7] but also with the number of siblings,[8-13] a purported measure of exposure to infections.

If the presence of older siblings protects children against the subsequent development of allergic disease by exposing them to more infections during early childhood, then attendance at day care should have a similar effect. Children attending day care are known to have more frequent infections than those who remain at home.[14-16] However, the results of studies examining the effect of attendance at day care on the development of allergic disease are conflicting. In one study, day-care attendance during infancy was found to protect against the development of asthma, hay fever, and skin-test reactivity among children with few siblings,[17] but in several other studies no association was found between attendance at day care and the subsequent development of allergic diseases.[9,13,18]

Interpretation of the available data regarding day-care attendance and the subsequent development of asthma is further complicated by the existence of multiple possible causes of wheezing during childhood.[19] Wheezing in preschool children is primarily associated with infections, whereas in school-age children it is primarily associated with atopy.[19,20] Although many children have wheezing during their preschool years, it is difficult to identify those who will later have asthma.[21] Therefore, increased exposure to other children may place preschool children at increased risk for wheezing associated with respiratory infections, but it may also help to protect them from IgE-associated wheezing later in childhood. Attendance at day care was found to be a risk factor for recurrent wheezing and asthma in children less than 5 years of age,[16,22] but among children 5 to 14 years old the frequency of asthma was inversely associated with previous day-care attendance.[17] In this study, we examined exposure to children at home and attendance at day care during infancy in relation to the subsequent development of asthma and frequent wheezing in a cohort of children followed prospectively from birth.

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METHODS

Study Population

We enrolled 1246 normal newborn infants in the Tucson Children's Respiratory Study between 1980 and 1984.[23] Detailed information on the enrollment process and study design has been published elsewhere.[23,24] Information about the mother's level of education, whether there was a history of asthma in either parent, the smoking status of the mother during the prenatal period, and the race of each parent was obtained from responses on questionnaires administered to parents soon after their child's birth. Information about breast-feeding status was obtained from two sources: prospectively from data gathered at health-supervision visits and retrospectively from responses on a follow-up questionnaire.[25]

The study was approved by the Human Subjects Committee of the University of Arizona. Written informed consent was obtained from parents at the time of enrollment and at each in-depth evaluation (which took place at years 6 and 11 of the study).

Siblings and Day Care

Parents reported information on all household members shortly after their child's birth. Because 95 percent of the children less than 18 years of age who were living at home were siblings of the enrolled child, all such children were considered siblings. Information about attendance at day care and about the number of unrelated children present in the day-care setting during the first three years of life was obtained for 996 children by means of a questionnaire administered to the parents from 1988 to 1990, when the mean (±SD) age of the children was 6.7±1.5 years.[14] Day care was defined as a child-care setting where six or more unrelated children were present.

Asthma and Frequent Wheezing

The parents of the enrolled children completed questionnaires related to their children's respiratory status at years 6, 8, 11, and 13 of the study (mean age of the children, 6.3±0.9, 8.6±0.7, 10.9±0.6, and 13.5±0.6 years, respectively). Children who had been given a diagnosis of asthma by a physician and who had had an exacerbation of their asthma during the previous year, as indicated by the responses on the questionnaires at any of these times, were categorized as having asthma. Parents were also asked on the questionnaires at years 6, 8, 11, and 13 whether their child's chest had ever sounded "wheezy" or "whistling" during the previous year and, if so, how often this had occurred.

Frequent wheezing was defined as the occurrence of more than three episodes of wheezing during the previous year. Data on frequent wheezing at years 2 and 3 (mean age of the children, 1.6±0.8 and 2.9±0.9 years, respectively) were also obtained, in a slightly different format: the parents were asked whether their child had had wheezing during the previous year and, if so, how often he or she had wheezed on a scale from 1 to 5, on which 1 indicated "very rarely" and 5 "on most days." Children with scores of 2 or higher in either year 2 or 3 were defined as having frequent wheezing during that year. Data on the frequency of upper respiratory tract infections were also obtained from these six questionnaires by asking parents the question, "During the past year, how many head colds (common colds) did this child have?"

Skin-Test Reactivity and Serum IgE Measurement

At years 6 and 11, skin tests were conducted with extracts of allergens common in the Tucson area (Hollister–Stier Laboratories, Everett, Wash.). At year 6, 737 children underwent skin testing with extracts of house-dust mix, the mold alternaria, Bermuda grass, careless weed (*Amaranthus palmeri*), mesquite, mulberry, and olive. At year 11, 663 children, 585 of whom had been tested at year 6, were tested with the same allergens as well as extracts of cat dander and *Dermatophagoides farinae*. The skin tests were read after 20 minutes, and the results were considered positive if a wheal at least 3 mm larger than the control wheal was produced. Children with a positive result on skin testing at either year 6 or year 11 were considered to have skin-test reactivity.

Serum IgE concentrations were measured at years 6 and 11 with paper radioimmunosorbent assays (Pharmacia Diagnostics, Piscataway, N.J.). Serum IgE concentrations above the 95th percentile for age (161 IU per milliliter at year 6 and 570 IU per milliliter at year 11) were considered high.[26] Children with a high serum IgE value at either year 6 or year 11 were considered to have a high serum IgE concentration.

TABLE 1. PERCENTAGE OF CHILDREN WITH ASTHMA ACCORDING TO THE NUMBER OF OLDER SIBLINGS AND THE AGE AT ENTRY INTO DAY CARE.

VARIABLE	NO. OF CHILDREN*	ASTHMA	RELATIVE RISK (95% CI)†	P VALUE
		%		
No. of older siblings‡				
0	405	21	1.0	
1	385	19	0.9 (0.7–1.0)	0.04
2	176	14	0.7 (0.5–1.0)	0.04
≥3	69	13	0.6 (0.4–1.0)	0.04
Age at entry into day care				
>12 mo	899	19	1.0	
7–12 mo	28	18	0.9 (0.4–2.1)	0.88
Birth to 6 mo	69	9	0.4 (0.2–1.0)	0.03

*The parents of 1035 children completed at least one of the questionnaires at years 6, 8, 11, and 13. Information about attendance at day care during the first three years of life was obtained for 996 children.

†The relative risk of asthma associated with each number of siblings was calculated from the ordinal variable by Cox regression analysis. CI denotes confidence interval.

‡P=0.03 by the Mantel–Haenszel chi-square test for trend.

Statistical Analysis

We used chi-square tests to assess statistical significance in bivariate analyses. Because significant linear trends in the incidence of asthma according to the number of siblings were identified in cross-sectional analysis, the number of siblings was considered a single ordinal variable in Cox regression analysis, and the crude relative risk of asthma according to the number of siblings was calculated. Adjusted relative risks of asthma were calculated in Cox regression analysis that included all potential confounding variables (sex, whether there was a history of asthma in either parent, the race of the parents, the mother's level of education, the mother's smoking status during the prenatal period, and breast-feeding status). In separate Cox regression analyses that included the same confounding variables, the adjusted relative risks of asthma and of frequent wheezing at years 6, 8, 11, and 13 were calculated.

We used the generalized estimating equation to assess the longitudinal effects of the number of siblings and day-care attendance on the prevalence of frequent wheezing from years 2 through 13. The generalized estimating equation is a statistical procedure that yields estimates of risk for longitudinal dichotomous data in mixed-effects regression models.[27] To be included in the longitudinal analysis, children were required to have complete information on at least one of the six questionnaires. To test the main hypothesis, we used a model in which frequent wheezing in each of the six questionnaire intervals was the outcome variable and day-care attendance or the presence of two or more older siblings was the exposure variable, with adjustment for the potential confounding variables listed above. To assess age-dependent associations, age was entered into the model as an independent variable, along

TABLE 2. PERCENTAGE OF CHILDREN WITH ASTHMA, HIGH SERUM IgE CONCENTRATIONS, AND SKIN-TEST REACTIVITY, ACCORDING TO THE NUMBER OF SIBLINGS AND DAY-CARE ATTENDANCE BEFORE THE AGE OF SIX MONTHS.*

OUTCOME	NO. OF CHILDREN	TWO OR MORE OLDER SIBLINGS OR DAY CARE	ONE OR NO OLDER SIBLINGS AND NO DAY CARE	RELATIVE RISK (95% CI)	P VALUE
		no./total no. (%)			
Asthma	985	36/289 (12)	144/696 (21)	0.6 (0.4–0.8)	0.002
High serum IgE	630	52/196 (27)	153/434 (35)	0.8 (0.6–1.0)	0.03
Skin-test reactivity†					
Any allergen	782	110/229 (48)	313/553 (57)	0.8 (0.7–1.0)	0.03
Alternaria	789	40/231 (17)	139/558 (25)	0.7 (0.5–1.0)	0.02

*Denominators are the numbers of children for whom data were available for the given outcome. CI denotes confidence interval.

†Seven children had negative results on skin tests with alternaria but did not have a complete set of skin tests. They were therefore excluded from the analysis of skin-test reactivity to any allergen but were included in the analysis of skin-test reactivity to alternaria.

with an interaction term for the degree of exposure to other children and the age of the child at the time the questionnaire was administered. All statistical tests were two-sided.

RESULTS

The parents of 1035 of the 1246 children in the original cohort completed at least one of the questionnaires at years 6, 8, 11, and 13, and these 1035 children were therefore included in the cross-sectional analyses of the development of asthma and frequent wheezing. The children included in these analyses were significantly more likely to have one sibling or no siblings, a mother with a high level of education, and white parents than were the children who were excluded because of missing information (data not shown). The parents of 875 children completed at least 1 questionnaire (mean, 5.3 questionnaires) and provided information on day-care attendance, and these 875 children were therefore included in the longitudinal analysis of frequent wheezing. The children included in the longitudinal analysis were similar to the 1035 children included in the cross-sectional analyses, except that they were significantly more likely to have white parents than were those excluded because of missing information (data not shown).

There was an inverse association between the incidence of asthma and both the number of older siblings present in the home at birth and the age at entry into day care (Table 1). This relation did not vary according to the sex of the siblings. Since there was no significant difference between day-care entry between the ages of 7 and 12 months and entry after the age of 12 months, these two categories were combined in subsequent analyses.

The incidence of asthma among children who had two or more older siblings or who attended day care during the first six months of life was significantly lower than that among children who had one sibling or no siblings and who did not attend day care (Table 2). The same children had a significantly lower prevalence of high serum IgE concentrations, skin-test reactivity to any allergen, and skin-test reactivity to alternaria, the allergen most commonly associated with asthma in the Tucson area.[28]

In a multivariate analysis, each additional older sibling and attendance at day care during the first six months of life remained inversely associated with the development of asthma (Table 3). Male sex and a history of asthma in the mother or the father were positively associated with the development of asthma in the child.

We also calculated the adjusted relative risks of asthma and frequent wheezing at years 6, 8, 11, and 13 among children who had two or more older siblings or who attended day care during the first six months of life, as compared with children who had one or no older siblings and who did not attend day care (Fig. 1). The protective effect of greater exposure

TABLE 3. SIGNIFICANT PREDICTORS OF ASTHMA IN 926 CHILDREN.

VARIABLE	ADJUSTED RELATIVE RISK (95% CI)*	P VALUE
Each additional older sibling	0.8 (0.7–1.0)	0.04
Entry into day care at ≤6 mo of age	0.4 (0.2–1.0)	0.04
Male sex	1.5 (1.1–2.0)	0.02
History of asthma in the mother	2.3 (1.6–3.3)	<0.001
History of asthma in the father	1.6 (1.1–2.4)	0.02

*In addition to the variables listed, the relative risks were adjusted for the mother's smoking status during the prenatal period, breast-feeding status, the race of the parents, and the mother's level of education. CI denotes confidence interval.

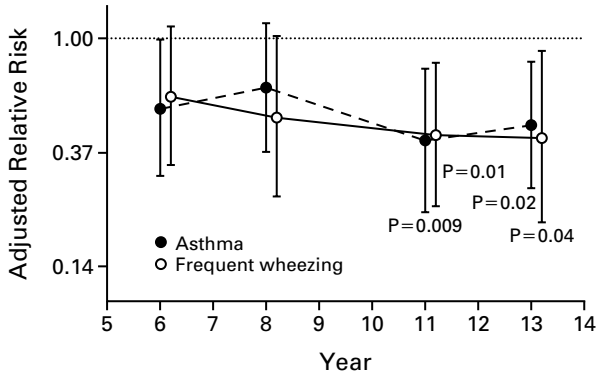

Figure 1. Adjusted Relative Risk of Asthma or Frequent Wheezing among Children Who Had Two or More Older Siblings or Who Attended Day Care during the First Six Months of Life, as Compared with Those with Less Exposure to Other Children.

Children with less exposure to other children were those who had one or no older siblings and who did not attend day care during the first six months of life. Relative risks were adjusted for sex, whether there was a history of asthma in the mother or the father, the mother's smoking status during the prenatal period, breast-feeding status, the parents' race, and the mother's level of education. The I bars represent the 95 percent confidence intervals. P values are for the comparisons between the children with greater exposure to others at home or at day care and those with less exposure. The adjusted relative risks are shown on a natural-log scale.

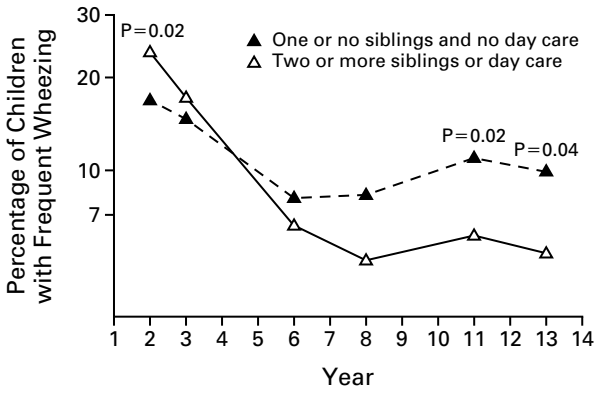

Figure 2. Prevalence of Frequent Wheezing among Children Who Had Two or More Older Siblings or Who Attended Day Care during the First Six Months of Life and among Children with Less Exposure to Other Children.

Children with less exposure to other children were those who had one or no older siblings and who did not attend day care during the first six months of life. P values are for the comparisons between the two groups of children. The results are shown on a logit scale.

to other children at home or at day care was similar for the two outcomes and appeared to be greater in the later years.

The occurrence of frequent wheezing among children in these two groups was also examined longitudinally for the entire study period. At year 2, the prevalence of frequent wheezing was significantly higher among children with greater exposure to other children at home or at day care than among those with less exposure to other children (24 percent vs. 17 percent, P=0.02), but at year 11 and year 13 it was significantly lower in the group with greater exposure (6 percent vs. 11 percent [P=0.02] and 5 percent vs. 10 percent [P=0.04], respectively) (Fig. 2).

The model based on the generalized estimating equation was used to examine the relative risk of frequent wheezing during the entire study period among those with greater exposure to other children at home or at day care as compared with those with less exposure, after adjustment for all potential confounding variables. Children who had greater exposure to others were more likely than those with less exposure to have frequent wheezing at year 2 (relative risk, 1.4; 95 percent confidence interval, 1.1 to 1.8; P=0.01) but were significantly less likely to have frequent wheezing at year 6 (relative risk, 0.8; 95 percent confidence interval, 0.6 to 1.0; P=0.03), year 8 (relative risk, 0.6; 95 percent confidence interval, 0.4 to 0.8; P=0.001), year 11 (relative risk, 0.4; 95 percent confidence interval, 0.3 to 0.6; P<0.001), and year 13 (relative risk, 0.3; 95 percent confidence interval, 0.2 to 0.5; P<0.001) (Fig. 3). When the data were analyzed in a separate model based on the generalized estimating equation, with the number of siblings and day-care attendance during the first six months of life entered as independent variables, similar trends for each variable were observed (data not shown).

DISCUSSION

The main finding of this study is that the development of asthma is less common among children with more exposure to other children at home or at day care during the first six months of life than among children with little or no exposure to other children at home or at day care. However, the children with more exposure had more frequent wheezing during the preschool years.

Decreasing family sizes and higher standards of personal hygiene, both of which result in a lower rate of cross-infection within households, have been suggested as explanations for the increase in allergic disease seen during the past 30 years.[10] While the frequency of asthma has increased, the percentage of young families in the United States with more than two children has declined, from 36 percent in 1970 to 21 percent in 1998.[29,30] During this same period, day-care attendance has increased, involving 60 percent of preschool children in 1995.[31] However, whereas 65 percent of four-year-old children attended a day-care center in 1995, only 7 percent of infants less

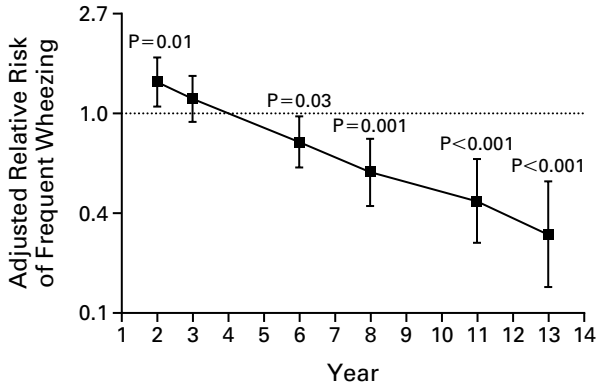

Figure 3. Adjusted Relative Risk of Frequent Wheezing among Children Who Had Two or More Older Siblings or Who Attended Day Care during the First Six Months of Life, as Compared with Children Who Had Less Exposure to Other Children, According to Analysis with the Generalized Estimating Equation.

Relative risks were adjusted for sex, whether there was a history of asthma in the mother or father, the mother's smoking status during the prenatal period, breast-feeding status, the race of the parents, and the mother's level of education. The I bars represent the 95 percent confidence intervals. P values are for the comparisons between the children with greater exposure to others at home or at day care and those with less exposure. The adjusted relative risks are shown on a natural-log scale.

than a year old did so.[31] Day-care attendance is also lowest among children from low-income families, among whom morbidity from asthma is high.[32]

Although children attending day care are at increased risk for many types of infections, the results of previous investigations of day-care attendance and the risk of asthma or recurrent wheezing are conflicting. However, when those results are viewed according to the ages at which the children were studied, they are consistent with the results of our study and with each other. Among two-year-old children, day-care attendance increased the risk of recurrent wheezing, and among four-to-five-year-old children, day-care attendance also increased the risk of asthma.[16,22] Among seven-year-old children, asthma was not associated with previous day-care attendance.[13,18] Among 5-to-14-year-old children, asthma was inversely associated with previous day-care attendance.[17] The current results demonstrate the same age-dependent relation between exposure to other children at home or at day care and the development of wheezing illnesses later in childhood. Although day-care attendance during the first six months of life is a risk factor for wheezing associated with lower respiratory tract infections early in life, it appears to protect against wheezing associated with atopy later in childhood.

The mechanism by which exposure to other children early in life might prevent the development of allergic disease, including asthma, is not known. Bacterial or viral infections occurring during infancy as a result of exposure to numerous children may provide important signals to the newborn's maturing immune system.[4] Within the first six months of life, the immune response of children without atopy shifts from one associated predominantly with type 2 helper T cells (Th2 cells), like that in adults with atopic illnesses, toward one based more on cytokines derived from type 1 helper T cells (Th1 cells), like that in adults without atopy.[33] Th1-like response includes the production of interferon-γ, which inhibits the proliferation of Th2 cells. Therefore, infections that stimulate a Th1-like response during this critical period of maturation may play an important part by inhibiting the predominantly Th2 response that is present in newborn infants.[4,33] The absence of such inhibitory signals during infancy may allow the expansion and maturation of Th2 memory cells, resulting in the persistence of a more atopic phenotype.

Alternative explanations for our results appear to be less plausible. Parents participating in our study may have confused symptoms of upper respiratory tract infections in their children with wheezing, in which case the excess wheezing during the school years among children who had had less contact with other children during infancy may simply represent "catch-up" infections that are due to their lower degree of acquired immunity. However, the findings reported here are specific to asthma and frequent wheezing: although children with one or no siblings and no early attendance at day care had more upper respiratory tract infections at year 6 than children with greater exposure to others during the preschool years, this difference gradually disappeared, becoming nonexistent by year 13 (data not shown). It is also possible that the two groups of children differed according to the presence of some other putative risk factor for asthma, such as exposure to allergens.[34] However, the primary allergen associated with asthma in this region of Arizona, alternaria, is ubiquitous. It also seems unlikely that allergen exposure would vary according to sibling order.

There are two possible weaknesses of this study. First, data on the occurrence of asthma and frequent wheezing were based on parents' responses on questionnaires. However, in other analyses of the same cohort, we found that these outcome measures correlated well with objective measures of bronchial hyperresponsiveness, such as peak-flow variability and the results of cold-air challenge or methacholine challenge.[19,35] Second, the data regarding day-care attendance were obtained retrospectively. However, the decision to enroll an infant in day care, the selection of a site, and often the mother's accompanying return to work usually make these events very memorable to the parents. Nevertheless, if misclassification of day-care status did occur, it would most likely have skewed our results toward the null hypothesis.

In conclusion, the results of this prospective, lon-

gitudinal study indicate that a young child's exposure to other children in or out of the home leads to more frequent wheezing during the first few years of life. However, such exposure protects against the development of asthma and frequent wheezing later during childhood.

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