Day Care Attendance, Respiratory Tract Illnesses, Wheezing, Asthma, and Total Serum IgE Level in Early Childhood

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Background: It has been hypothesized that day care–related infections may explain the inverse relation between day care attendance in early life and asthma in childhood.

Objective: To examine the relation between day care attendance or respiratory tract illnesses in the first year of life and wheezing and asthma in the first 4 years of life among children with a parental history of atopy who were followed up from birth.

Results: Day care attendance in the first year of life was inversely associated with geometric mean total serum IgE level (12.9 [±1 SD = 3.3, 51.4] IU/mL for day care vs 18.5 [±1 SD = 5.3, 64.7] IU/mL for no day care; P = .03) at 2 years of age but not significantly associated with wheezing at or after 2 years of age. Having at least 1 physician-diagnosed lower respiratory tract illness in the first year of life was significantly associated with recurrent wheezing (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.0-4.1) and asthma (OR, 2.5; 95% CI, 1.1-5.5) at 4 years of age, but not with any wheezing (infrequent and frequent) at 3 years or older. Illnesses of the upper respiratory tract (≥1 physician-diagnosed upper respiratory tract illness or ≥3 episodes of nasal catarrh) in the first year of life were associated with any wheezing (frequent and infrequent) between the ages of 1 and 4 years, but not with recurrent wheezing or asthma at 4 years of age.

Conclusions: Our results suggest that among children with a parental history of atopy the protective effect of day care attendance in early life against the development of atopy has begun by 2 years of age, and that a protective effect of day care attendance in early life against wheezing may not be observed until after 4 years of age.

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The prevalence of asthma in the United States has increased significantly during the past 30 years, making this respiratory disease a major public health problem.1,2 It has been hypothesized that the asthma epidemic in the United States and other developed countries is due, at least in part, to reduced exposure to other children3 and a decreased risk for infections in early childhood.4 Approximately 60% of children in the United States attended day care in 1995.5 Results of 2 recent studies conducted in Germany6 and the United States7 have demonstrated an inverse association between day care attendance in early life and the development of atopy,4 wheezing,7 and asthma1 later in childhood. Since day care attendance is associated with an increased risk for infectious illnesses of the upper (URI)8 and lower respiratory tract (LRI)9,10 in early life, these infectious illnesses may be partly responsible for the observed protective effect of day care attendance on the development of childhood asthma.

The Home Allergens and Asthma Study is a prospective birth cohort study of children with a parental history of asthma or allergies in the Boston, Mass, metropolitan area. We previously showed that day care attendance among study participants was associated with an increased risk for physician-diagnosed URIs and LRIs in the first year of life.11 In the present report, we examine the association between day care attendance in the first year of life and wheezing and asthma in the first 4 years of life and try to determine whether the observed association is due primarily to day care–related respiratory tract illnesses requiring medical attention.

RESULTS

CHARACTERISTICS OF THE COHORT AND DAY CARE EXPERIENCE

The characteristics of the 498 study subjects have been described in detail else-
PATIENTS AND METHODS

The 505 infants with a history of allergy or asthma in at least 1 parent were recruited between September 1, 1994, and August 31, 1996. The screening and recruitment of families have been described elsewhere. Every 2 months, beginning when the child was 2 months of age, a telephone questionnaire was administered to the child’s primary caretaker until the child’s second birthday. Afterwards, interviews were conducted every 6 months. Of the 505 children, 7 were excluded because they were followed up for no more than 4 months during their first year of life. The study was approved by the institutional review board of Brigham and Women’s Hospital, Boston.

Day care attendance in the first year of life was treated as a binary variable. Every 2 months during the child’s first year of life, the caretaker was asked: “Since we last spoke with you on [date given], has your child had a pneumonia diagnosed by a doctor?” Other bimonthly questions included whether a runny or stuffed nose or physician-diagnosed croup, bronchitis, bronchiolitis, ear infection, or sinus trouble had occurred since the previous questionnaire was administered. These variables were then categorized as any vs no physician-diagnosed LRIs (ie, croup, bronchitis, bronchiolitis, or pneumonia), any vs no physician-diagnosed URIs (ie, ear infection and sinus trouble), and at least 3 vs fewer than 3 reports of runny or stuffed nose (nasal catarrh). Sociodemographic and familial variables included the child’s race and annual household income, type of medical insurance (none, private, and nonprivate), in utero exposure to smoking, breast-feeding (as a binary and a categorical variable {never, exclusively for ≤4 months, and exclusively for ≥4 months}), bottle-feeding in a bed or crib before bedtime, parental history of asthma (ever diagnosed and ever diagnosed with current symptoms), number of older siblings (as a continuous and as a categorical variable {<3 vs ≥3}), and average number of cigarettes per day smoked by all adults in the household.

Wheezeing was considered present at any time from 12 to 48 months of age if at least 1 affirmative response was given to the question: “Since we last spoke with you on [date given], has your child had wheezing or whistling in the chest?” Every year—starting at 2 years of age—we also asked: “How many attacks or episodes of wheezing has your child had in the past 12 months?” Recurrent wheezing at 4 years of age was defined as at least 2 episodes of wheezing in the previous 12 months. Asthma at 4 years of age was defined as physician-diagnosed asthma and at least 1 episode of wheezing in the 12 months preceding the interview.

Total serum IgE level at 2 years of age was measured by an enzyme-immunoassay based on the sandwich technique (UniCAP; Pharmacia Diagnostics, Kalamazoo, Mich). All values were converted to the log-natural scale for analysis.

We conducted the bivariate analysis using χ² and 2-tailed t-test. We used stepwise logistic regression to study the relation between day care attendance in the first year of life and the outcomes of interest (total serum IgE level at 2 years of age, and recurrent wheezing and asthma at 4 years of age) while adjusting for potential confounders and examining interactions. In the final models, we included those variables that satisfied a change-in-estimate criterion (≥10% in the odds ratio [OR]) or that were significant at the P < .05 level. For the longitudinal analysis of the relation between day care attendance in the first year of life and wheezing in the first 4 years of life, we used proportional hazard models, with repeated events on the same child being handled by the method of Anderson and Gill. To examine age-dependent associations, we calculated interaction terms between the age of the children at each survey and the variables in the model.

where. Table 1 summarizes the main characteristics of the study participants.  Of the 238 children (47.8%) who attended day care in their first year of life, 161 (67.6%) attended in a home setting; 52 (21.8%), a nonresidential setting; and 25 (10.5%), both (mixed day care). Among these 238 children, 50 (21.0%) attended day care with at least 10 children. All 238 children attended day care for at least 5 hours per week and for at least 1 month; 109 (45.8%) attended day care for at least 6 months, at least 3 days per week, and at least 4 hours per day. Of the 498 study participants, 461 (92.6%) were followed up to 4 years of age. No statistically significant differences in sex, day care attendance in the first year of life, respiratory tract illnesses in the first year of life, and parental history of asthma were found between those with and without 4-year follow-up. Subjects who dropped out of the study before 4 years of age were significantly more likely to come from low-income families and to not be breastfed in the first year of life than subjects who underwent 4 years of follow-up. Of the 498 participating children, 230 (46.2%) underwent a measurement of total serum IgE level at 2 years of age. No significant differences in day care attendance or respiratory tract illnesses in the first year of life were found between those with and without total serum IgE measurements at 2 years of age.

RELATION BETWEEN DAY CARE ATTENDANCE OR RESPIRATORY TRACT ILLNESSES IN THE FIRST YEAR OF LIFE AND RECURRENT WHEEZING AND ASTHMA AT AGE 4 YEARS

As in our previous study, the amount of time that the children spent in day care during the first year of life was not associated with the outcomes of interest. Since the estimates of the association between day care attendance in the first year of life and the outcomes of interest were similar, whether the child attended day care in the first or second 6 months of life, we combined attendance in the first and second 6 months of life.

Table 2 summarizes the results of the analysis of the relation between day care attendance or respiratory tract illnesses in the first year of life and recurrent wheezing and asthma at 4 years of age. There was no significant association between day care attendance in the first year of life and recurrent wheezing or asthma at 4 years of age. Although children who had at least 1 physician-diagnosed LRI in the first year of life had increased odds of having recurrent wheezing or asthma at 4 years of age, we found no significant association between URIs (physician-diagnosed URIs or ≥3 episodes of nasal catarrh) in the first year of life and recurrent wheezing or asthma.
at 4 years of age. We found no association between the number of older siblings and recurrent wheezing or asthma at 4 years of age.

To examine whether the association between physician-diagnosed LRIs in the first year of life and recurrent wheezing or asthma at 4 years of age was due to reverse causation, we repeated the multivariate analysis after excluding children who wheezed in the first year of life. Among the 280 children who did not have any wheezing episodes in the first year of life, there was no significant association between physician-diagnosed LRIs in the first year of life and recurrent wheezing (OR, 1.7; 95% confidence interval [CI], 0.5-5.8) or asthma (OR, 0.4; 95% CI, 0.1-3.8) at 4 years of age.

LONGITUDINAL ANALYSIS OF THE RELATION BETWEEN DAY CARE ATTENDANCE OR RESPIRATORY TRACT ILLNESSES IN THE FIRST YEAR OF LIFE AND ANY WHEEZING IN THE FIRST 4 YEARS OF LIFE

The results of the multivariate longitudinal analysis of the relation between day care attendance or respiratory tract illnesses in the first year of life and the primary caretaker’s report of wheezing (infrequent and frequent) throughout the first 4 years of life are summarized in Table 3. We found a significant interaction between day care attendance or physician-diagnosed LRIs in the first year of life and age. The risk for wheezing associated with day care attendance in the first year of life decreased with increasing age, with no significant day care–related risk for wheezing at 2 years of age. Although the risk for wheezing associated with physician-diagnosed LRIs in the first year of life decreased significantly with age, the risk for wheezing associated with physician-diagnosed URIs or at least 3 episodes of nasal catarrh in the first year of life was increased throughout the first 4 years of life.

Table 2. Relation Between Day Care Attendance or Physician-Diagnosed Infectious Lower Respiratory Tract Illnesses in the First Year of Life and Recurrent Wheezing and Asthma at 4 Years of Age*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Recurrent Wheezing (n = 40)</th>
<th>Asthma (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Day care attendance, first year of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (52.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>19 (47.5)</td>
<td>1.0 (0.5-1.8)</td>
</tr>
<tr>
<td>Physician-diagnosed LRI, first year of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>23 (57.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (42.5)</td>
<td>2.2 (1.2-4.4)</td>
</tr>
<tr>
<td>Physician-diagnosed URI, first year of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11 (27.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (72.5)</td>
<td>1.5 (0.7-3.1)</td>
</tr>
<tr>
<td>≥3 Episodes of nasal catarrh (runny nose), first year of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Yes</td>
<td>40 (100.0)</td>
<td>...</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval. Other abbreviations and definitions are given in the first footnote to Table 1.†Adjusted also for sex, household income, bottle-feeding in the bed or crib before bedtime in the first year of life, maternal history of asthma with current symptoms, maternal cigarette smoking during pregnancy, and either day care attendance or physician-diagnosed LRIs in the first year of life.‡P<.05.§No odds ratio was calculated since none of the subjects without recurrent nasal catarrh had recurrent wheezing.
The geometric mean (± 1 SD) total serum IgE level at 2 years of age was significantly lower in children who attended day care in their first year of life than that in children who did not (12.9 [3.3, 51.4] IU/mL vs 18.5 [5.3, 64.7] IU/mL; P = .03). This difference was not significantly changed after adjusting for sex and household income. There was no significant association between physician-diagnosed respiratory tract illnesses or at least 3 episodes of nasal catarrh in the first year of life and the children’s total serum IgE level at 2 years of age.

In our study, having at least 1 physician-diagnosed LRI in the first year of life was associated with increased odds of recurrent wheezing and asthma at 4 years of age. Reverse causation is a plausible explanation for our findings, as the observed association between physician-diagnosed LRIs in the first year of life and recurrent wheezing or asthma at 4 years of age was no longer significant once children who wheezed in the first year of life were excluded from the analysis. Thus, children who are true asthmatic patients may be predisposed to infectious LRIs in early life. An alternative explanation for our findings is that some of the LRIs in our study may have been due to respiratory syncytial virus, an infectious illness that is associated with wheezing in early life16 and up to 11 years of age.17 Our findings are in agreement with those of 2 longitudinal birth cohort studies of Norwegian18 and German14 children. In the Norwegian study, a strong association was found between parental report of infectious LRIs in infancy and asthma at 4 years of age.19 The German investigators found a strong association between infectious LRIs in the first 3 years of life and asthma and current wheezing at 7 years of age.14 This association was no longer significant, however, when wheezing LRIs were excluded from the analysis.

We found that having at least 1 physician-diagnosed LRI in the first year of life was associated with an increased risk for infectious respiratory tract illnesses in the first year of life11 but inversely associated with a marker of atopy at 2 years (total serum IgE level), it may not be possible to observe a protective effect of day care attendance in early life on wheezing until the children are older.

In our study, longest day care attendance in the first year of life decreased significantly after adjusting for sex and household income. There was no significant association between physician-diagnosed respiratory tract illnesses or at least 3 episodes of nasal catarrh in the first year of life and the children’s total serum IgE level at 2 years of age.

Our study is unique in that we included detailed information on exposure to day care and URIs and LRIs in the first year of life, a time when exposure to day care or respiratory tract infections may influence the development of the immune system.6,7,14 Among children with parental history of atopy, the risk for wheezing associated with day care attendance in the first year of life decreased significantly with age. At 2 years of age, day care attendance in the first year of life was inversely associated with total serum IgE level, but not significantly associated with wheezing.

In a longitudinal birth cohort study, children with greater exposure to older siblings at home or day care were more likely to have frequent wheezing at 2 years of age, but significantly less likely to have frequent wheezing or a high total serum IgE level at 6 years of age than those with less exposure to other children.7 Cross-sectional studies of German6 and Italian15 children also showed an inverse association between day care attendance in early life and atopy6 and persistent wheezing at school age.15 Our longitudinal finding of an inverse association between day care attendance in the first year of life and total serum IgE level among children with a parental history of atopy suggests that the protective effect of day care attendance in early life on the development of atopy has begun by 2 years of age. The lack of a significant inverse association between day care attendance in the first year of life and asthma or wheezing at 4 years of age in our study is likely because wheezing in early childhood may be related to infections in children with small airways or to allergic inflammation of the airways.15 Since day care attendance in our study was positively associated with an increased risk for infectious respiratory tract illnesses in the first year of life11 but inversely associated with a marker of atopy at 2 years (total serum IgE level), it may not be possible to observe a protective effect of day care attendance in early life on wheezing until the children are older.

In our study, having at least 1 physician-diagnosed LRI in the first year of life was associated with increased odds of recurrent wheezing and asthma at 4 years of age. Reverse causation is a plausible explanation for our findings, as the observed association between physician-diagnosed LRIs in the first year of life and recurrent wheezing or asthma at 4 years of age was no longer significant once children who wheezed in the first year of life were excluded from the analysis. Thus, children who are true asthmatic patients may be predisposed to infectious LRIs in early life. An alternative explanation for our findings is that some of the LRIs in our study may have been due to respiratory syncytial virus, an infectious illness that is associated with wheezing in early life16 and up to 11 years of age.17 Our findings are in agreement with those of 2 longitudinal birth cohort studies of Norwegian18 and German14 children. In the Norwegian study, a strong association was found between parental report of infectious LRIs in infancy and asthma at 4 years of age.19 The German investigators found a strong association between infectious LRIs in the first 3 years of life and asthma and current wheezing at 7 years of age.14 This association was no longer significant, however, when wheezing LRIs were excluded from the analysis.

We found that having at least 1 physician-diagnosed LRI in the first year of life was associated with an increased risk for wheezing (infrequent and frequent wheeze) at 1 and 2 years of age but not at 3 or 4 years of age. This finding is likely explained by airway growth resulting in a decreased risk for wheezing related to infectious LRIs in early life, particularly among children with infrequent wheezing and no maternal history of asthma.19

We found that URIs (physician-diagnosed URIs or ≥3 episodes of nasal catarrh) in the first year of life were significantly associated with wheezing (infrequent and frequent) from 1 to 4 years of age, but not with asthma at 4 years of age. However, we found a nonstatistically significant trend for an association between at least 3 episodes of nasal catarrh in the first year of life and recurrent wheezing at 4 years of age, as none of the children who had fewer than 3 episodes of nasal catarrh in the first year of life had
Day care attendance in early life is inversely related to atopy and asthma among children of school age. Little is known about the relation between day care attendance or respiratory tract illnesses in early life and wheezing and asthma in early childhood, particularly among children with a parental history of atopy.

Our findings among children with parental history of atopy suggest that an inverse relationship exists between day care attendance in early life and atopy by 2 years of age, but that any inverse association between day care attendance in early life and wheezing may not be evident until after 4 years of age. In children at high risk for atopy, the positive association between illnesses of the upper and lower respiratory tract and wheezing in the first 4 years of life may be due to infections and/or be the early manifestation of an atopic predisposition.

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