

Day Care Attendance in Early Life, Maternal History of Asthma, and Asthma at the Age of 6 Years

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Among children not selected on the basis of a parental history of atopy, day care attendance in early life is inversely associated with asthma at school age. We examined the relation between day care in the first year of life and asthma, recurrent wheezing, and eczema at the age of 6 years and wheezing in the first 6 years of life among 453 children with parental history of atopy followed from birth. Among all study participants, day care in the first year of life was inversely associated with eczema (odds ratio [OR] = 0.3, 95% confidence interval [CI] = 0.1–0.8). Day care attendance in early life was associated with a decreased risk of asthma (OR = 0.3, 95% CI = 0.1–0.7) and recurrent wheezing (OR = 0.3, 95% CI = 0.1–0.9) at the age of 6 years and with a decreased risk of any wheezing after the age of 4 years only among children without maternal history of asthma. Among children with maternal history of asthma, day care in early life had no protective effect on asthma or recurrent wheezing at the age of 6 years but was instead associated with an increased risk of wheezing in the first 6 years of life. Our findings suggest that maternal history of asthma influences the relation between day care–related exposures and childhood asthma.

Keywords: day care; maternal history; asthma

The prevalence of asthma in the U.S. increased significantly from the 1960s to the 1990s, making this respiratory disease a major public health problem (1, 2). It has been postulated that the asthma epidemic in the United States and other developed countries is due, at least in part, to reduced exposure to other children (3) and a decreased risk of infections in early childhood (4).

Approximately 60% of children in the United States attended day care in 1995 (5). Day care attendance in early life has been shown to be inversely associated with atopy (6), wheezing (7), and asthma (7) later in childhood. Because day care attendance is associated with an increased risk of infectious illnesses of the upper (8) and lower (9) respiratory tract in early life, it is possible that these infectious illnesses are partly responsible for the protective effect of day care attendance on the development of asthma.

The Home Allergens and Asthma Study is a prospective birth cohort study of children with a history of asthma, hay fever, or allergies in at least one parent. We previously found

that day care attendance in early life was associated with an increased risk of doctor-diagnosed respiratory illnesses in the first year of life (10) but a decreased total serum IgE level at age 2 years (11). In this report, we examine the relation between day care attendance in the first year of life and asthma and wheezing in the first 6 years of life. Because maternal history of asthma may influence the relation between environmental exposures and asthma and wheezing in childhood (12, 13), we were interested in further examining the relation between day care attendance in early life and wheezing and asthma in children with and without maternal history of asthma.

METHODS

The 505 infants with parental history of atopy were recruited between September 1994 and August 1996. The screening and recruitment of families have been described previously (14, 15). In brief, eligibility criteria included residence inside route 128 (a highway encircling the Boston metropolitan area); maternal age greater than or equal to 18 years; history of hay fever, asthma, or allergies in either parent; and maternal ability to speak English or Spanish. Families were not screened if the newborn was hospitalized in the intensive care unit, if his/her gestational age was less than 36 weeks, or if he/she had a congenital anomaly. Every 2 months, beginning when the child was 2 months old, 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, seven were excluded because they were followed for 4 months or less during their first year of life. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Day care attendance in the first year of life was treated primarily as a binary variable (10). The type of day care was classified as home (at the day care provider's residence), nonresidential (not provided at someone else's home), and mixed. Day care was also classified according to the number of children attending day care with the study participant (< 10 vs. ≥ 10) (10). A detailed description of the other variables considered for inclusion in the multivariate analysis is provided in the online supplement.

Wheezing was considered present at any time point between 12 and 72 months if there was an affirmative response 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 the age of 2 years—we also asked, "How many attacks or episodes of wheezing has your child had in the past 12 months?" At the age of 6 years, recurrent wheezing was defined as two or more episodes of wheezing in the previous year; asthma as physician-diagnosed asthma and one or fewer episodes of wheezing in the previous year; allergic rhinitis as physician-diagnosed allergic rhinitis and a history of nasal discharge or sneezing apart from colds in the previous year; and eczema as physician-diagnosed eczema and a history of a pruritic rash in the previous year.

The bivariate analysis was conducted using χ^2 and two-tailed *t* tests. Stepwise logistic regression was used to study the relation between day care in the first year of life and asthma, recurrent wheezing, allergic rhinitis, and eczema at the age of 6 years while adjusting for potential confounders and examining interactions. For the longitudinal analysis of the relation between day care in the first year of life and wheezing in the first 6 years of life, we used proportional hazard models, with re-

(Received in original form September 17, 2002; accepted in final form November 16, 2002)

Supported by grant AIEHS35786 from the National Institutes of Health. J.C.C. is supported by grant KO1 HL04370-01A1.

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This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Am J Respir Crit Care Med Vol 167, pp 1239–1243, 2003

Originally Published in Press as DOI: 10.1164/rccm.200209-1063OC on November 21, 2002
Internet address: www.atsjournals.org

TABLE 1. DAY CARE ATTENDANCE IN THE FIRST YEAR OF LIFE AND ASTHMA, RECURRENT WHEEZING, AND ECZEMA AT THE AGE OF 6 YEARS

	Asthma (n = 38)			Recurrent Wheezing (n = 41)			Eczema (n = 33)		
	No. (%)	Unadjusted	Adjusted*	No. (%)	Unadjusted	Adjusted*	No. (%)	Unadjusted	Adjusted†
Day care, first year									
No	22 (9.4)	1.0	1.0	27 (11.5)	1.0	1.0	24 (10.3)	1.0	1.0
Yes	16 (7.3)	0.8 (0.4–1.5)	0.7 (0.3–1.4)	14 (6.5)	0.5 (0.3–1.0)	0.5 (0.2–1.0)‡	9 (4.2)	0.4 (0.2–0.8)	0.3 (0.1–0.8)
One or more physician-diagnosed LRI, first year									
No	18 (5.4)	1.0	1.0	24 (7.3)	1.0	1.0	29 (8.8)	1.0	1.0
Yes	20 (16.7)	3.5 (1.8–6.9)	3.5 (1.8–7.2)	17 (14.2)	2.1 (1.1–4.1)	2.1 (1.1–4.2)	4 (3.4)	0.4 (0.1–1.0)	0.4 (0.1–1.3)

Definition of abbreviations: LRI = lower respiratory illness.

Data are reported as odds ratio (OR) (95% confidence interval (CI)).

* Adjusted for sex of child, maternal history of asthma, and bottle feeding before sleep time in the first year of life, in addition to the variables listed in the column.

† Adjusted for race and parental history of eczema, in addition to the variables listed in the column.

‡ $p < 0.05$.

peated events on the same child being handled by the method of Andersen and Gill (16) and adjustment for correlations between these repeated events handled using methods described by Therneau and Grambsch (17).

RESULTS

The characteristics of the 498 study subjects have been described in detail elsewhere (10, 11). Of the 238 children (47.8%) who attended day care in their first year of life, 161 (67.6%) went to a home setting, 52 (21.8%) to a nonresidential setting, and 25 (10.5%) to both (mixed day care). Of the 238 children who attended day care, 161 (67.6%) attended day care with at least four children, and 50 (21.0%) attended day care with at least 10 children. All of the 238 children who attended day care in their first year of life did so for 5 hours or more per week and for at least 1 month. Of the 238 children, 109 (45.8%) attended day care for 6 months or more, 3 days or more per week, and 4 hours or more per day (10).

Of the 498 study participants, 468 (94%) and 453 (90.9%) were followed up to the ages of 3 and 6 years, respectively. There was no statistically significant difference in day care attendance in the first year of life between those with and without 6-year follow-up (48.1 vs. 44.4%, $p = 0.64$). Subjects who dropped out of the study before the age of 6 years were significantly more likely to come from low-income families.

As in previous studies (10, 11), the amount of time that the children spent in day care (treated as either a continuous [number of months] or a categorical [< 3 , 3–6, and > 6 months] variable) did not appreciably change the relation between day care in the first year of life and the outcomes of interest. Because 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, day care attendance in the first and second 6 months of life was combined (10).

Table 1 summarizes the results of the analysis of the relation between day care attendance in the first year of life and asthma, recurrent wheezing, and eczema at the age of 6 years. After adjustment for potential confounders, day care attendance in the first year of life was significantly associated with decreased odds of recurrent wheezing and eczema at the age of 6 years. In these multivariate models, having at least one doctor-diagnosed lower respiratory illness (LRI) in the first year of life was significantly associated with increased odds of asthma and recurrent wheezing at the age of 6 years.

We found no significant association between day care attendance in the first year of life and allergic rhinitis at the age of 6 years (unadjusted odds ratio = 1.0, 95% confidence interval [CI] = 0.5–1.7).

We found that neither the type of day care (home/mixed vs. non-residential) nor the number of children attending day care significantly influenced the relation between day care attendance in the first year of life and asthma, recurrent wheezing, or eczema at the age of 6 years. There was no significant association between the number of older siblings and asthma, recurrent wheezing, or eczema at the age of 6 years.

We found no significant association between paternal history of asthma and asthma or recurrent wheezing at the age of 6 years, as well as no significant interaction between paternal history of asthma and day care attendance in the first year of life in a multivariate model. Because of a statistically significant interaction between day care attendance in the first year of life and maternal history of asthma ($p < 0.01$) in the multivariate analysis and our *a priori* hypothesis that maternal history may influence the relation between day care attendance and asthma or recurrent wheezing, the analysis was repeated after stratifying by maternal history of asthma (Table 2). Among children without maternal history of asthma, day care attendance in the first year of life was inversely associated with recurrent wheezing and asthma at the age of 6 years. Among children with maternal history of asthma, there was a nonstatistically significant trend for a positive association between day care attendance in the first year of life and asthma—but not recurrent wheezing—at the age of 6 years. Neither maternal history of asthma nor parental history of eczema significantly influenced the relation between day care attendance in the first year of life and eczema at the age of 6 years.

The results of the multivariate longitudinal analysis of the relation between day care attendance in the first year of life and the primary caretaker's report of wheezing (infrequent and frequent) throughout the first 6 years of life are summarized in Figure 1. Among all children (Figure 1A), there was a significant interaction between day care attendance in the first year of life and age. The risk of wheezing associated with day care in the first year of life decreased with increasing age, with no significant day care-related risk of wheezing at the age of 2 years (risk ratio [RR] = 1.2, 95% CI = 0.9–1.6) and a decreased risk of wheezing by the age of 6 years (RR = 0.6, 95% CI = 0.4–1.0, $p = 0.05$). However, the relation between day care attendance in the first year of life and wheezing in the first 6 years of life was significantly influenced by the child's maternal history of asthma. Among children without maternal history of asthma (Figure 1B), the risk of wheezing associated with day care attendance in the first year of life decreased with increasing age (p for interaction with age < 0.01). Day care attendance in the first year of life was inversely associated with wheezing starting at the age of 4 years (RR = 0.7, 95% CI = 0.5–1.0, $p = 0.04$), and there was

TABLE 2. RELATION BETWEEN DAY CARE IN THE FIRST YEAR OF LIFE AND ASTHMA AND RECURRENT WHEEZING AT AGE 6 YEARS AFTER STRATIFYING BY MATERNAL HISTORY OF ASTHMA

	Asthma			Recurrent Wheezing		
	No. (%)	Unadjusted	Adjusted*	No. (%)	Unadjusted	Adjusted*
No maternal history of asthma (n = 322)						
Day care, first year of life						
No	19 (11.2)	1.0	1.0	20 (11.9)	1.0	1.0
Yes	5 (3.3)	0.3 (0.1–0.7)	0.3 (0.1–0.7)	7 (4.6)	0.4 (0.1–0.9)	0.3 (0.1–0.9)
One or more physician- diagnosed LRIs, first year of life						
No	12 (5.0)	1.0	1.0	16 (6.7)	1.0	1.0
Yes	12 (14.8)	3.3 (1.4–7.7)	3.4 (1.4–8.3)	11 (13.6)	2.2 (1.0–5.0)	2.1 (0.9–5.0)
Maternal history of asthma (n = 131)						
Day care, first year of life						
No	3 (4.6)	1.0	1.0	7 (10.6)	1.0	1.0
Yes	11 (16.9)	4.3 (1.1–16.1)	3.7 (0.9–14.5)	7 (10.9)	1.0 (0.3–3.1)	0.9 (0.3–2.9)
One or more physician- diagnosed LRIs, first year of life						
No	6 (6.5)	1.0	1.0	8 (8.8)	1.0	1.0
Yes	8 (20.5)	3.7 (1.2–11.5)	3.3 (1.0–11.2) [†]	6 (15.4)	1.9 (0.6–5.9)	1.8 (0.6–5.9)

For definition of abbreviation, *see* Table 1.

Data are reported as odds ratio (95% confidence interval).

* Adjusted for sex of child and bottle feeding before sleep time in the first year of life, in addition to the variables listed in the column.

[†] $p = 0.05$.

a strong inverse association between day care attendance in the first year of life and wheezing at the age of 6 years (RR = 0.4, 95% CI = 0.2–0.7). Among children with maternal history of asthma (Figure 1C), day care attendance in the first year of life was associated with an increased risk of wheezing in the first 6 years of life that did not change significantly with increasing age (RR = 1.6, 95% CI = 1.0–2.5, $p = 0.05$).

DISCUSSION

Previous studies of children not selected on the basis of a parental history of atopy have shown an inverse association between day care attendance in early life and asthma, wheezing, and allergy in childhood (6, 7, 18). Among children with parental history of asthma, hay fever, or allergies, we found an inverse association between day care attendance in early life and an allergic disease (eczema) at the age of 6 years. However, a significant inverse association between day care attendance in early life and asthma and recurrent wheezing at the age of 6 years and any wheezing after the age of 4 years was found only among children without maternal history of asthma. To our knowledge, this is the first study to show that maternal history may influence the relation between day care attendance in early life and childhood asthma.

The inverse association between day care attendance in the first year of life and asthma and wheezing among children without maternal history of asthma was independent of the relation between doctor-diagnosed LRIs in the first year of life and asthma, suggesting that in these children the protective effect of day care on the development of asthma and atopy may be mediated by exposure to mild-to-moderate infectious illnesses not diagnosed by a physician. In support of this hypothesis, Illi and colleagues showed that infections in early life that did not affect the lower respiratory tract and that were presumably viral (not confirmed by cultures) were inversely associated with the risk of asthma in school age children, perhaps through stimulation of the immature immune system toward the Th1 phenotype (19). Alternatively, our findings may be explained by other exposures encountered in day care centers. Endotoxin, a proinflammatory

substance present in the cell walls of gram-negative bacteria, could exist in abundance in day care settings where children, cats, dogs, rugs, or dust are present (20). Because exposure to endotoxin has been inversely associated with decreased allergen sensitization (21–23) and atopic asthma (22) in recent cross-sectional studies of infants (21) and children of school age (22, 23), exposure to high endotoxin levels in day care may also explain our results.

We did not observe an inverse association between day care attendance in the first year of life and asthma or recurrent wheezing at the age of 6 years among children with maternal history of asthma. Although the nonstatistically significant trend for an association between day care in early life and asthma—but not recurrent wheezing—at the age of 6 years may be explained by an earlier diagnosis of asthma among children whose mothers have asthma and who have frequent day care–related wheezing LRIs (“diagnostic bias”), this is not likely to be the sole explanation of our findings, as we also found a positive association between day care attendance in the first year of life and any wheezing in the first 6 years of life.

Even though the number of children with maternal history of asthma and complete follow-up was relatively small ($n = 111$), our findings suggest that maternal history of asthma influences the relation between day care–related exposures and childhood asthma through yet-unidentified genetic factors and/or early-life environmental exposures shared by mother and child. Because maternal history of asthma influenced the relation between day care and asthma and wheezing but had no effect on the observed inverse association between day care and eczema, it is also plausible that day care–related exposures have airway-specific effects in early life that are dependent of whether the child’s mother has asthma.

We recognize several limitations to our findings. First, most of the children participating in the study attended day care in home settings with a relatively small number of other children and thus may have encountered a more modest burden of infectious and noninfectious exposures than children attending non-residential day care centers. However, the experience of children

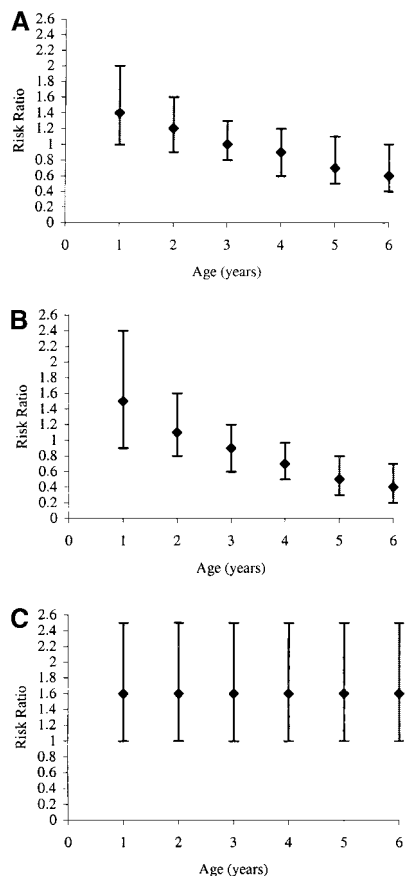


Figure 1. (A) Adjusted risk ratio of wheezing between the ages of 1 and 6 years for children who attended day care in the first year of life compared with children without exposure to day care in the first year of life. Risk ratios were adjusted for sex, household income, maternal history of asthma, having at least one doctor-diagnosed lower respiratory illness in the first year of life, recurrent nasal catarrh, and bottle feeding before sleep time in the first year of life. (B) Adjusted risk ratio of wheezing between the ages of 1 and 6 years among children without maternal history of asthma who attended day care in the first year of life compared with children without maternal history of asthma without exposure to day care in the first year of life. Risk ratios were adjusted for sex, household income, and having at least one doctor-diagnosed lower respiratory illness in the first year of life. (C) Adjusted risk ratio of wheezing between the ages of 1 and 6 years among children with maternal history of asthma who attended day care in the first year of life compared with children with maternal history of asthma without exposure to day care in the first year of life. Risk ratios were adjusted for sex, having at least one doctor-diagnosed lower respiratory illness in the first year of life, and maternal smoking during pregnancy. For A and B, the risk of wheezing associated with exposure to day care in the first year of life changed significantly between the ages of 1 and 6 years (p for interaction with age ≤ 0.01). Error bars represent the 95 percent confidence intervals.

in our cohort reflects that of children living in the greater Boston area, where approximately 76% of licensed day care is provided in a home setting (10). Second, we assessed the presence of respiratory illnesses in early life by parental report and did not measure asymptomatic infections. Among children with parental history of atopy, illnesses of the respiratory tract may be due to infection, allergy, or both. Thus, the observed association between LRIs in the first year of life and asthma at age 6 years may be due to “reverse causation” (children who are “true asth-

matics” may be predisposed to LRIs in early life) and/or to infectious LRIs (e.g., those due to respiratory syncytial virus) associated with an increased risk of childhood wheezing (24). Third, our results are not generalizable to the general population in the greater Boston area because we selected a stable population with parental history of asthma or allergies. Our findings, however, are applicable to a group at high risk for the development of allergic diseases.

In summary, our results suggest that maternal history of asthma influences the relation between day care attendance in the first year of life and asthma and wheezing in the first 6 years of life among children with parental history of atopy. Among children with parental history of atopy but no maternal history of asthma, day care attendance in early life was inversely associated with asthma and recurrent wheezing at the age of 6 years and with any wheezing at or after the age of 4 years. Among children with maternal history of asthma, day care attendance in early life had no apparent protective effect on asthma or recurrent wheezing at the age of 6 years but was instead associated with an increased risk of wheezing in the first 6 years of life.

Acknowledgment: The authors would like to thank the participating families for their enthusiastic collaboration and Ms. Jaylyn Olivo for her editorial assistance.

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