

Original article

Respiratory illnesses in early life and asthma and atopy in childhood

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Background: The relation between respiratory illnesses in early life and the development of asthma and atopy in childhood is incompletely understood.

Objective: We sought to examine the relationship between respiratory illnesses in early life and atopic diseases at school age.

Methods: We performed a prospective birth cohort study of the relationship between respiratory illnesses in the first year of life and asthma, atopy (sensitization to ≥ 1 allergen), and allergic rhinitis at school age in 440 children with a parental history of atopy. Logistic regression was used to examine the relationship between respiratory illnesses and asthma, atopy, and allergic rhinitis. The relationship between respiratory illnesses in early life and repeated measures of wheezing between the ages of 1 and 7 years was investigated by using a proportional hazards models.

Results: Physician-diagnosed croup (adjusted odds ratio [OR], 0.30; 95% CI, 0.12-0.72) and having 2 or more physician-diagnosed ear infections (adjusted OR, 0.58; 95% CI, 0.35-0.98) in the first year of life were inversely associated with atopy at school age. Physician-diagnosed bronchiolitis before age 1 year was significantly associated with asthma at age 7 years (adjusted OR, 2.77; 95% CI, 1.23-6.22). Recurrent nasal catarrh (≥ 3 episodes of a runny nose) in the first year of life was associated with allergic rhinitis at age 7 years (adjusted OR, 2.99; 95% CI, 1.03-8.67).

Conclusion: The relationship between early-life respiratory illnesses and asthma and atopy is complex and likely dependent on the type of infection and immune response it initiates.

Clinical implications: Certain respiratory illnesses in early life modify the risk of atopy and asthma at school age. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Bronchiolitis, croup, ear infections, wheezing, asthma, allergy, skin tests

Asthma affects an estimated 9 million children in the United States.¹ In this country a significant proportion of cases of asthma are diagnosed before the age of 6 years,² and most children with asthma are sensitized to at least one common allergen (ie, atopic).^{3,4} Thus there has been considerable interest in understanding the relation between early-life exposures and asthma and atopy in childhood.

Respiratory infectious illnesses, mostly viral, are very common in early life. The relation between respiratory infectious illnesses in early life and asthma in childhood is incompletely understood. Exposure to respiratory infectious illnesses in early life might increase⁵ or decrease⁶ the risk of asthma in childhood, perhaps depending on host factors and the location, timing, and type of microbial exposure.

Bronchiolitis, most commonly caused by respiratory syncytial virus (RSV), is the most common lower respiratory tract illness (LRI) in early life.⁷ Among children not selected on the basis of a high risk of asthma, RSV-induced bronchiolitis in early life has been associated with subsequent wheezing and childhood asthma.^{5,8-11} Controversy exists regarding the mechanism or mechanisms for this association. For example, RSV-induced bronchiolitis has been associated with atopy in some studies^{8,12,13} but not in others.^{5,9,11,14}

The relation between respiratory infectious illnesses other than RSV-induced bronchiolitis and asthma and atopy has been less extensively studied. Most studies of the relation between severe or recurrent croup in early life and asthma were retrospective and yielded conflicting results.¹⁵⁻¹⁷ Physician-diagnosed viral infectious upper respiratory tract illnesses (URIs) in early life have been associated with a reduced risk of asthma and atopy in some studies⁶ but not in others.¹⁸ Little is known about the relation between respiratory illnesses in early life and asthma in children at high risk for asthma and atopy.

The Epidemiology of Home Allergens and Asthma Study is a prospective birth cohort study designed to examine potential risk factors for asthma and allergic diseases in a group at high risk for these outcomes. In this report we examine the relation between respiratory illnesses in the first year of life and asthma and atopy at school age.

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The Epidemiology of Home Allergens and Asthma Study is supported by National Institutes of Health (NIH) grant AIEHS35786 to Dr Gold. Dr Celedón is supported by NIH grants HL04370 and HL073373. Dr Ramsey is supported by the Department of Medicine of the University of Manitoba, a Canada sponsorship award, and NIH/National Heart, Lung, and Blood Institute Training grant 5 T32 HL07427.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication May 4, 2006; revised September 11, 2006; accepted for publication September 13, 2006.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2006.09.012

Abbreviations used

LRI: Lower respiratory tract illnesses
 OR: Odds ratio
 RSV: Respiratory syncytial virus
 URI: Upper respiratory tract illnesses

METHODS**Study cohort**

Five hundred five infants with a history of asthma or allergies in at least one parent were recruited between September 1994 and August 1996. Details of the screening process and eligibility criteria have been described in detail previously.¹⁹ Briefly, eligibility criteria included living within the limits of route 128, which surrounds the city of Boston; maternal age of 18 years or older; and history of allergies, asthma, or hay fever in either parent. Children were excluded if they were admitted to the neonatal intensive care unit, were less than 36 weeks of gestational age, or had any congenital abnormalities. Mothers gave consent for eligibility screening during their initial hospitalization, and then gave consent for participation in a longitudinal study at the time of the first home visit. Every 2 months, beginning when the child was 2 months of age, a telephone questionnaire (modified from the American Thoracic Society Division of Lung Diseases questionnaire)²⁰ was administered to the child's primary caretaker until the child's second birthday. Afterward, interviews were conducted every 6 months. Of the 505 children initially enrolled in the study, 7 were excluded because they participated in the study for 4 or fewer months during their first year of life, resulting in a final cohort of 498 children. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Definition of predictor variables

Every 2 months in the first year of life, the primary caretaker was asked, "Since we last spoke with you on [date given], has your child had an ear infection diagnosed by a doctor?" Other bimonthly questions regarding respiratory illnesses included whether any of the following had occurred since the previous questionnaire was administered: a runny or stuffed nose, physician-diagnosed sinus trouble, and physician-diagnosed LRIs (pneumonia, bronchiolitis, bronchitis, or croup). If any of the previously listed respiratory illnesses occurred, then additional information was obtained regarding need for hospitalization. Parental report of each physician-diagnosed respiratory illness was analyzed separately (eg, physician-diagnosed bronchiolitis) and as a composite variable for both physician-diagnosed URIs (sinus trouble or ear infections) and physician-diagnosed LRIs (pneumonia, bronchiolitis, bronchitis or croup). Nasal catarrh and physician-diagnosed ear infections in the first year of life were categorized as previously described: 3 or more versus less than 3 episodes of a runny nose (recurrent nasal catarrh) and 2 or more versus less than 2 physician-diagnosed ear infections.²¹

The following variables were considered for inclusion in the multivariable models: sociodemographic and familial factors, such as the child's race, annual household income, and paternal and/or maternal history of asthma (ever and ever with current symptoms [active])^{22,23}; paternal and/or maternal history of hay fever, perinatal factors (eg, the child's gestational age),²⁴ birth weight, season of birth, maternal age, *in utero* exposure to tobacco smoke, breast-feeding (ever), bottle feeding the child in the bed or crib before sleeptime (ordinal variable, ranging from 0-6 reports),²¹ and number of older siblings (age ≤ 14 years); and relevant exposures in the first year of life, such as the average number of cigarettes smoked per day by

all adults in the household, day-care attendance,²⁵ use of antibiotics,²⁶ and exposure to a pet cat or dog in the home.²⁷

Allergy testing

At a mean age of 7.4 years (range, 6.5-10.1 years), allergy skin testing was performed in 248 children, and levels of IgE specific to common allergens were measured in an additional 23 children.

Skin testing was performed on the volar aspect of the lower arms. The allergens tested included common indoor (cat dander, dog dander, cockroach [*Blatella germanica*], house dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], and mouse epithelial extract) and outdoor (ragweed, tree, *Aspergillus* species, *Alternaria* species, grass, *Cladosporium* species, and *Penicillium* species) allergens (Hollister Steir Laboratories, Spokane, Wash). Glycerinated saline and histamine were used as the negative and positive controls, respectively. Skin test results to specific allergens were considered positive if the mean diameter of the wheal was 3 mm or greater after subtraction of the saline control wheal.

Sera from 23 children who declined skin testing were assayed for IgE levels to the allergens listed above using the UniCAP 250 system (Pharmacia & Upjohn, Kalamazoo, Mich). IgE levels to specific allergens were considered positive at a level of 0.35 IU/mL or greater.

Outcome definitions

We used 2 types of outcomes: end points at age 7 years (or school age) and repeated measures of wheeze over the course of follow-up. At age 7 years, asthma was defined as physician-diagnosed asthma and at least 1 episode of wheezing in the previous year, recurrent wheezing (an alternative definition of asthma) was defined as at least 2 episodes of wheezing in the previous year, allergic rhinitis was defined as physician-diagnosed allergic rhinitis and nasal discharge or sneezing apart from colds in the previous year, and atopy was defined as at least 1 positive skin test result or specific IgE measurement to the allergens tested. For the longitudinal analysis of repeated measures of wheeze, wheezing was considered present at any time between 12 and 84 months of age if an affirmative response was given to the following question: "Has your child had wheezing or whistling in the chest since we last spoke?"

Statistical methods

Bivariate relationships between the predictor and outcome variables were analyzed by using χ^2 tests for categorical variables and 2-tailed *t* tests for a categorical and continuous variable. Logistic regression was used to study the relation between respiratory illnesses in the first year of life and the end points of interest (asthma, recurrent wheezing, allergic rhinitis, and atopy) while adjusting for potential confounders and examining potential interactions. Variables other than respiratory illnesses were considered for inclusion in the final models by using a combination of statistical tools, such as stepwise regression and biologic considerations. In the final models variables were included if they were significant at a *P* value of less than .05 or satisfied a change-in-estimate criterion ($\geq 10\%$ change in the odds ratio [OR]).

The longitudinal relationship between respiratory illnesses in the first year of life and repeated measures of wheeze between ages 1 and 7 years was analyzed by using a proportional hazards model, in which repeated events in the same child were handled by using the method of Andersen and Gill²⁸ and adjustment for correlations between repeated events was handled by using the methods described by Therneau and Grambsch.²⁹ Follow-up time in months was used as the time variable. The same criteria for inclusion of variables in the logistic regression models were applied to the longitudinal models. S-PLUS software (version 3.4; Mathsoft, Inc, Cambridge, Mass) was used for the longitudinal analysis, and the SAS software package (SAS Institute, Inc, Cary, NC) was used for all other analyses.

TABLE I. Characteristics of participating children

Variable	Baseline (n = 498)	At age 7 y (n = 440)	Children with allergy testing at school age (n = 271)
Sex			
Male	268 (53.8)	240 (54.5)	155 (57.2)
Female	230 (46.2)	200 (45.5)	116 (42.8)
Race/ethnicity			
White	375 (75.3)	351 (79.8)*	219 (80.8)*
Black	60 (12.1)	36 (8.2)*	23 (8.5)*
Hispanic	28 (5.6)	21 (4.8)	11 (4.1)
Other	35 (7.0)	32 (7.3)	18 (6.6)
Income†			
≥\$30,000	439 (90.7)	403 (93.7)*	251 (95.1)*
<\$30,000	45 (9.3)	27 (6.3)	13 (4.9)
Pneumonia in the first year of life‡	14 (2.8)	10 (2.3)	7 (2.6)
Bronchiolitis in the first year of life‡	65 (13.1)	56 (12.7)	35 (12.9)
Bronchitis in the first year of life‡	21 (4.2)	17 (3.9)	12 (4.4)
Croup in the first year of life‡	57 (11.5)	52 (11.8)	30 (11.1)
Any LRI in the first year of life‡	132 (26.5)	117 (26.6)	70 (25.8)
Sinus trouble in the first year of life‡	43 (8.6)	39 (8.9)	23 (8.5)
≥2 ear infections in the first year of life‡	186 (37.3)	161 (36.6)	104 (38.4)
Recurrent nasal catarrh (≥3 episodes of a runny nose) in the first year of life	421 (84.5)	371 (84.3)	229 (84.5)
Any URI in the first year of life‡	423 (65.1)	284 (64.6)	177 (65.3)
Ever breast-fed in the first year of life	372 (74.7)	337 (76.6)	202 (74.5)
Maternal history of asthma (ever)	152 (30.5)	130 (29.6)	76 (28.0)
Paternal history of asthma (ever)§	116 (23.7)	100 (23.2)	61 (22.8)
Maternal smoking <i>in utero</i>	33 (6.6)	24 (5.5)	21 (7.8)
Attended day care in the first year of life	238 (47.8)	207 (47.2)	140 (51.7)
No. of older siblings (age ≤14y)			
0	228 (45.8)	215 (48.9)	136 (50.2)
1	176 (35.3)	150 (34.1)	93 (34.3)
≥2	94 (18.9)	75 (17.0)	42 (15.5)*
No. of antibiotic courses in first year of life			
0	146 (29.3)	133 (30.2)	80 (29.5)
1	111 (22.3)	97 (22.1)	58 (21.4)
≥2	241 (48.4)	210 (47.7)	133 (49.1)

Any LRI, Pneumonia, bronchiolitis, bronchitis, or croup; any URI, sinus trouble or ear infections.

* $P < .05$ compared with the baseline group.

†Missing data on 14 subjects.

‡All parental report of physician-diagnosed illnesses.

§Missing data on 8 subjects.

RESULTS

The characteristics of the 498 study subjects have been described in detail elsewhere.²² Of the 498 study participants, 440 (88.4%) were followed up to the age of 7 years, and 271 (54.4%) had an assessment of allergic sensitization at school age. Children who dropped out of the study before age 7 years were more likely to be of nonwhite ethnicity and to be from a family with an average household income of less than \$30,000 per year (Table I). There were no significant differences in the frequency of any respiratory illness in the first year of life between subjects who were followed to age 7 years and those who dropped out ($P > .3$ in all cases, except for physician-diagnosed pneumonia [$P = .07$]). Similar results were obtained for the comparison of children with and without assessment of allergic sensitization (Table I). There was no significant

difference in the frequency of respiratory illnesses in the first year of life between those with allergy testing and those without ($P > .6$ for all respiratory illnesses).

Of the 56 children with physician-diagnosed bronchiolitis in the first year of life, 10 (17.9%) had asthma at age 7 years. In contrast, only 33 (8.6%) of the 394 children without physician-diagnosed bronchiolitis in the first year of life had asthma at age 7 years. Very few children required hospitalization for either bronchiolitis (6 or 10.7%) or croup (2 or 3.8%).

The analysis of the relation between respiratory illnesses in the first year of life and asthma and recurrent wheezing at age 7 years is shown in Table II. Physician-diagnosed bronchiolitis was the only respiratory illness significantly associated with asthma and recurrent wheezing at age 7 years. Antibiotic use in the first year of life was not significantly associated with asthma or recurrent wheezing

TABLE II. Respiratory illnesses in the first year of life and asthma* and recurrent wheezing* at age 7 years

Variable (reference group)	OR and 95% CI			
	Asthma (n = 43)		Recurrent wheezing (n = 38)	
	Bivariate	Multivariable†	Bivariate	Multivariable‡
Pneumonia§ (no)	2.37 (0.49-11.55)	—	1.17 (0.14-9.50)	—
Bronchiolitis§ (no)	2.31 (1.07-5.00)	2.77 (1.23-6.22)	2.32 (1.04-5.21)	2.61 (1.14-5.94)
Bronchitis§ (no)	NA	—	NA	—
Croup§ (no)	1.24 (0.50-3.09)	—	0.86 (0.29-2.53)	—
Any LRI§ (none)	1.74 (0.90-3.35)	—	1.48 (0.73-2.99)	—
Sinus trouble§ (no)	1.40 (0.52-3.81)	—	1.68 (0.61-4.59)	—
Any ear infection§ (none)	0.67 (0.36-1.26)	—	0.92 (0.47-1.83)	—
≥2 ear infections§ (<2)	0.92 (0.48-1.78)	—	0.89 (0.44-1.80)	—
Any URI§ (none)	0.60 (0.32-1.13)	—	0.84 (0.42-1.66)	—
Recurrent nasal catarrh (<3 episodes)	0.67 (0.31-1.47)	—	1.26 (0.47-3.35)	—

NA, Unable to calculate because there were no patients with asthma who also had bronchitis.

*Asthma was defined as physician-diagnosed asthma and wheezing in the previous year. Recurrent wheezing was defined as at least 2 episodes of wheezing in the previous year.

†Adjusted for sex, number of times bottle fed in crib, income less than \$30,000 versus \$30,000 or greater, maternal history of asthma ever, and paternal history of asthma ever.

‡Adjusted for sex and income less than \$30,000 versus \$30,000 or greater.

§All parental report of physician-diagnosed illnesses.

||*P* < .05.

at age 7 years. There was no significant modification of the effect of bronchiolitis on asthma by parental history of asthma or atopy.

On bivariate longitudinal analysis, physician-diagnosed bronchiolitis in the first year of life was associated with an increased risk of wheezing between ages 1 and 7 years (hazard ratio, 1.84; 95% CI, 1.30-2.61), which did not change significantly over time (*P* value for time interaction = .67). After adjustment for other significant variables and potential confounders (sex, household income, maternal age, attending day care or having ≥2 older siblings, and gestational age), bronchiolitis in the first year of life remained a significant predictor of wheezing between ages 1 and 7 years (hazard ratio, 1.85; 95% CI, 1.32-2.59). There was no significant modification of the effect of bronchiolitis on wheezing between ages 1 and 7 years by parental history of asthma or atopy.

The results of the bivariate and multivariable analysis of the relation between respiratory illnesses in the first year of life and atopy are shown in Table III. After adjustment for sex and household income, 2 separate physician-diagnosed respiratory illnesses in the first year of life (croup and having at least 2 ear infections) were inversely associated with atopy at school age. There was no significant association between antibiotic use in the first year of life and atopy at school age.

Table IV shows the results of the analysis of the relation between respiratory illnesses in the first year of life and allergic rhinitis at age 7 years. After adjustment for potential confounders, recurrent nasal catarrh in the first year of life was associated with a 3-fold increase in the odds of allergic rhinitis at age 7 years. Similar (but nonstatistically significant, given a relatively small sample size) results were obtained when we used a more stringent definition of allergic rhinitis (allergic rhinitis [as previously defined] and

having at least 1 positive skin test result or specific IgE level to allergens).

DISCUSSION

Among children at risk for asthma and atopy, we found an inverse association between 2 physician-diagnosed illnesses (croup and recurrent ear infections) and atopy at school age.

Most studies of the relation between ear infections (eg, otitis media) and atopy have been cross-sectional.³⁰⁻³² Tainio et al³³ found a positive association between recurrent otitis media (≥5 episodes) in the first year of life and atopy at age 2 years; however, atopy was a combined end point consisting of asthma, atopic dermatitis, urticaria, allergic rhinitis, or food allergy. Another cross-sectional study using data from the Third National Health and Nutrition Examination Survey found that history of ear infections was positively associated with childhood asthma.³⁴ In a retrospective study Njå et al³⁵ found an inverse association between ear infections in infancy and atopy only among children with a parental history of atopy. Our study differs from that study and others in that data regarding ear infections were collected prospectively, thus avoiding the potential for recall bias. In addition, children in the study by Njå et al were recruited on the basis of the presence of asthma or wheezing. Ours is thus the first prospective study to report an inverse association between ear infections in infancy and atopy.

Ear infections in the first few years of life are mostly bacterial in cause, and the most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and β-hemolytic streptococci^{36,37}; these bacterial infections predominately stimulate T_H1

TABLE III. Respiratory illnesses in the first year of life and atopy* at school age

Variable (reference group)	Bivariate association		Multivariable model†	
	OR (95% CI)	P value	OR (95% CI)	P value
Pneumonia (no)‡	1.09 (0.24-4.99)	1.00	—	—
Bronchiolitis (no)‡	0.85 (0.42-1.73)	.65	—	—
Bronchitis (no)‡	0.26 (0.07-0.98)	.04	—	—
Croup (no)‡	0.31 (0.14-0.70)	.006	0.30 (0.12-0.72)	.007
Any LRI (none)‡	0.52 (0.30-0.90)	.02	—	—
Sinus trouble (no)‡	1.30 (0.54-3.12)	.66	—	—
Ear infection ever (no)‡	0.70 (0.43-1.16)	.17	—	—
≥2 ear infections (<2)‡	0.56 (0.34-0.92)	.021	0.58 (0.35-0.98)	.04
Recurrent nasal catarrh (<3 episodes of a runny nose)	0.80 (0.41-1.57)	.52	—	—
Any URI‡	0.75 (0.45-1.25)	.27	—	—

*At least 1 positive skin test result or specific IgE level to the allergens tested.

†Adjusted for income (<\$30,000 vs >\$30,000) and sex.

‡All parental report of physician-diagnosed illnesses.

immune responses.³⁸ Thus ear infections in early childhood might protect against atopy by stimulating maturation of the T_H1 immune response, leading to a more balanced T_H1/T_H2 system opposed to the predominance of T_H2 cells in infancy. Alternatively, bacterial pathogens causing ear infections might stimulate regulatory T cells, which modulate T_H1 and T_H2 immune responses, potentially protecting against the development of atopy.^{39,40}

To our knowledge, this is the first report of an inverse association between parental report of physician-diagnosed croup and atopy. In children not selected on the basis of parental history of asthma or allergies, 2 studies showed a positive relationship between recurrent croup (≥2 episodes) before the age of 10 to 11 years and atopy,^{41,42} whereas others have found no association.^{16,17,43} In the only other prospective cohort study, there was no association between croup during the first 3 years of life and atopy at age 6 or 11 years.⁴³

A plausible explanation for the discrepant findings between our study and others is that we focused on exposure to croup in the first year of life (when infections might have a more influential role in the development of an infant's immune system) and that children in our study were at high risk for atopy and thus could have a different immunologic response to infection. Recent results from the Childhood Origin of Asthma Study (COAST) showed that cytokine responses to viral infections in early life change significantly during the first year of life and alter the risk of development of wheezing in the first year of life among children at high risk of atopic diseases.⁴⁴ In addition, immunologic responses to viral infections were different depending on the severity of infection (wheezing vs nonwheezing) and were different between children with and without early markers of atopy.⁴⁴ We did see that the protective association between croup and atopy was strongest among those children with both croup and wheezing, which indicates more severe illnesses in the first year of life. The COAST study also found that low levels of IL-13 were associated with wheezing but not other atopic outcomes.⁴⁵ Thus there appear to be different immunologic risk factors for wheezing compared with

TABLE IV. Association between respiratory illnesses in the first year of life and allergic rhinitis* at age 7 years

Variable (reference group)	OR (95% CI)	
	Bivariate	Multivariable†
Pneumonia‡ (no)	0.65 (0.08-5.18)	—
Bronchiolitis‡ (no)	1.14 (0.53-2.46)	—
Bronchitis‡ (no)	0.36 (0.05-2.73)	—
Croup‡ (no)	1.30 (0.60-2.81)	—
Any LRI‡ (none)	1.01 (0.55-1.84)	—
Sinus trouble‡ (no)	0.85 (0.32-2.26)	—
Ear infection ever‡ (no)	1.28 (0.73-2.24)	—
≥2 ear infections‡ (<2)	1.13 (0.65-1.94)	—
Any URI‡ (none)	1.24 (0.70-2.19)	—
Maternal history of hay fever (no)	3.50 (1.84-6.66)	3.33 (1.74-6.38)§
Recurrent nasal catarrh (<3 episodes of a runny nose)	3.15 (1.10-8.96)	2.99 (1.03-8.67)

*Physician-diagnosed allergic rhinitis and naso-ocular symptoms apart from colds in the previous year.

†Also adjusted for lowest quartile of birth weight and the number of older siblings younger than 14 years in the home.

‡All parental report of physician-diagnosed illnesses.

§P < .001.

||P < .05.

other allergy outcomes, and possibly different immunologic responses elicited by specific respiratory illnesses in early life determine whether a child wheezes or develops atopy. An alternative explanation for our findings is “reverse causation” (eg, if children without wheezing, who were more likely to be nonatopic, were given diagnoses of croup more often than children with wheezing). However, this is unlikely because the direction of the association between croup and atopy in children who did (OR, 0.20; 95% CI, 0.05-0.74) and did not (OR, 0.44; 95% CI, 0.14-1.39) have any wheezing in the first year of life was the same. Finally, there might have been some misclassification of the diagnosis of croup because there were no cultures taken to confirm the diagnosis. However, the diagnosis of croup is

usually based on clinical criteria, and other investigations are infrequently performed.⁴⁶ If any misclassifications were present, it would likely be nondifferential and bias our results toward the null hypothesis.

Recurrent nasal catarrh in the first year of life was associated with increased odds of allergic rhinitis at age 7 years. Recurrent nasal catarrh might be an indicator of early allergic disease, or it might represent viral infections in early life. In the Tucson Children's Respiratory Study 77% of children with symptoms of rhinitis in the first year of life had physician-diagnosed allergic rhinitis at age 6 years, suggesting that recurrent nasal catarrh might be an early symptom of allergic rhinitis.⁴⁷ Our study differs from the Tucson study in that our cohort was selected based on a high risk of asthma and allergies.

Among children at risk for asthma and atopy, we found that physician-diagnosed bronchiolitis in the first year of life was associated with childhood asthma and wheezing. Sigurs et al¹² found that the risk of asthma after bronchiolitis requiring hospitalization was higher in children with a family history of asthma than in children without such a history. One other retrospective study demonstrated that a family history of atopy or asthma was more common in children with wheezing after RSV infection in the first year of life than in children without any further respiratory symptoms.⁴⁸ Our study is the first to examine the longitudinal relationship between bronchiolitis in the first year of life and asthma and wheezing at school age among children at high risk for asthma and allergies and is one of only 3 prospective cohort studies^{5,49} to look at nonhospitalized cases of bronchiolitis. Our results are consistent with those of studies of children from general population cohorts.^{5,8-11}

In agreement with the findings of prospective studies of children recruited from the general population, we did not find a significant association between physician-diagnosed bronchiolitis in the first year of life and atopy.^{5,9,11,14,50} Our findings further suggest that the relation between bronchiolitis and asthma is mediated by nonatopic mechanisms (eg, increased airway inflammation and airway reactivity). An alternative explanation for the observed association is that infants with lower lung function near birth are more susceptible to bronchiolitis and might then go on to have asthma or persistent wheezing in later childhood.⁴³

Our study has several limitations. First, the reported respiratory illnesses might be moderate to severe because they required parental report of a physician's diagnosis. However, unlike many prior studies, we included a significant proportion of patients who did not require hospitalization and therefore have a wider spectrum of disease severity.

Second, parental report of physician-diagnosed recurrent ear infections might not always represent recurrent otitis media. However, we have previously shown a strong association between day care and recurrent ear infections in the first year of life that was similar to that shown in a large study in which otitis media was diagnosed by means of pneumatic otoscopy and tympanometry.⁵¹

Third, because cultures were not obtained to determine the cause of a respiratory illness (eg, viral vs bacterial), there is potential misclassification of the exposures of

interest. However, the observed association between physician-diagnosed bronchiolitis in the first year of life and childhood wheezing and asthma is consistent with findings of studies in which viral cultures were obtained. Furthermore, few children with bronchiolitis were given diagnoses of other conditions in the first year of life (eg, only 4 [6.2%] of the 65 children with bronchiolitis were also given a diagnosis of bronchitis), suggesting that marked misclassification of bronchiolitis by physicians did not occur.

Fourth, few cases of pneumonia and bronchitis were reported in the first year of life, and therefore we might have been underpowered to detect an association between these LRIs and the outcomes of interest. However, the results of our study are consistent with prior studies showing that the respiratory illness most strongly associated with wheezing and asthma in childhood is bronchiolitis.

Fifth, allergy skin tests or specific IgE measurements were only obtained in a subset of the study participants, and this subgroup might not be entirely representative of the whole cohort. Although there could be differences in unmeasured confounders between children who did and did not have allergy skin testing or specific IgE measurements, selection bias is an unlikely explanation for our results because there were no significant differences in any of the exposures of interest (respiratory illnesses in the first year of life) between those with and without an assessment of allergic sensitization.

Finally, our results are not generalizable to children in the general population but are relevant to a group of children at high risk for the development of asthma and allergies. Because of the high prevalence of atopy among adults of reproductive age in industrialized countries (30% to 40%),^{52,53} our results are applicable to a substantial proportion of children in these nations.

In summary, our findings suggest that physician-diagnosed croup and physician-diagnosed ear infections in the first year of life protect against the development of atopy in children at risk for asthma and allergies. In these children recurrent nasal catarrh in the first year of life might be an early marker of allergic rhinitis, and bronchiolitis is a risk factor for the subsequent development of childhood asthma (likely through nonatopic mechanisms). Our overall results further suggest that the relation between respiratory illnesses in early life and asthma and atopy is complex and likely dependent on factors related to the host and the timing, severity, and etiology of the infectious exposure.

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