

Cohort Study of Severe Bronchiolitis during Infancy and Risk of Asthma by Age 5 Years



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What is already known about this topic? Severe bronchiolitis is a risk factor for childhood asthma. However, most studies of this association are small and from outside the United States.

What does this article add to our knowledge? We confirm that infants with severe bronchiolitis have an increased prevalence of childhood asthma. However, this prevalence is lower than in most prior studies.

How does this study impact current management guidelines? This study highlights the importance of future research to identify those children with severe bronchiolitis at highest risk of asthma to target therapies toward preventing asthma development.

BACKGROUND: Severe bronchiolitis (ie, bronchiolitis requiring hospital admission) is thought to markedly increase asthma risk, with 30%-50% developing asthma by age 5 years. To date, studies of this association are small, and most are from outside the United States.

OBJECTIVE: The objective of this study was to investigate the association between severe bronchiolitis and risk of asthma in a US birth cohort.

METHODS: We studied a cohort nested within the Massachusetts General Hospital Obstetric Maternal Study (MOMS), a prospective cohort of pregnant women enrolled during 1998-2006. Children of mothers enrolled in MOMS were included in the analysis if they received care within our health

system (n = 3653). Diagnoses and medications were extracted from the children's electronic health records; we also examined pregnancy and perinatal risk factors collected for the underlying pregnancy study.

RESULTS: The birth cohort was 52% male, 49% white, and 105 infants (2.9%) had severe bronchiolitis. Overall, 421 children (11.5%) developed asthma by age 5 years. Among the children with severe bronchiolitis, 27.6% developed asthma by age 5 years. In multivariable logistic regression adjusting for 12 risk factors, severe bronchiolitis remained a strong risk factor for developing asthma by age 5 years (odds ratio 2.57; 95% confidence interval 1.61-4.09).

Conclusions: In a large Boston birth cohort, the frequency of severe bronchiolitis and childhood asthma was similar to published data. Among children with severe bronchiolitis, the risk of developing asthma was lower than prior studies but still high (27.6%). This difference may be due to different study designs, populations, and outcome definitions studied. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:92-6)

Key words: Asthma; Atopic dermatitis; Bronchiolitis; Eczema; Prevalence; Respiratory syncytial virus; Risk factors; Wheezing

Severe bronchiolitis, or bronchiolitis requiring admission to the hospital, affects 2%-3% of all infants,^{1,2} which makes it a leading cause of hospitalization among infants.^{1,3} Published data suggest that as many as 30%-50% of these infants will develop asthma by age 5 years.^{4,5} However, much of the literature on severe bronchiolitis in infancy and risk of recurrent wheezing or childhood asthma comes from small case series,⁶⁻⁸ cohorts from outside the United States,⁶⁻⁹ or cohorts without control groups.^{9,10}

Asthma is common, affecting approximately 8% of all Americans, including more than 7 million US children.¹¹ Asthma prevalence among children was increasing in the early 2000s, but it appears to have plateaued in 2008 and possibly

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This work was supported by the National Institutes of Health grants T32 HL-116275, U01 AI-087881, R01 AI-114552, and R21 HL-129909.

The opinions expressed are those of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of interest: D. S. Balekian has received research support from the National Institutes of Health (Grant T32 HL116275). R. W. Linnemann declares no relevant conflicts of interest. K. Hasegawa has received research support from the National Institutes of Health and Teva. R. Thadhani has received consultancy fees and payment for developing educational presentations from Roche and ThermoFisher; and has a patent with ThermoFisher. C. A. Camargo Jr has received research support from the National Institutes of Health.

Received for publication March 21, 2016; revised June 30, 2016; accepted for publication July 1, 2016.

Available online August 11, 2016.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2016.07.004>

Abbreviations used

AD- Atopic dermatitis
CHD- Congenital heart disease
CI- Confidence interval
EHR- Electronic health record
ICD-9- International Classification of Diseases, Ninth Revision
MOMS- Massachusetts General Hospital Obstetric Maternal Study
NICU- Neonatal intensive care unit
NCQA- National Committee for Quality Assurance
OR- Odds ratio
RSV- Respiratory syncytial virus

declined in more recent years.¹² There are regional variations, however, with no change in prevalence among children of all age groups in the northeastern United States.¹²

The aims of this Boston-based cohort study were: (1) to report the frequency of severe bronchiolitis, (2) to report the frequency of asthma by age 5 years, both overall and among the subset of children with severe bronchiolitis, and (3) to determine the risk of developing asthma by age 5 years among those with and without severe bronchiolitis in infancy.

METHODS

Study design

We analyzed electronic health record (EHR) data collected on children born to mothers who were enrolled in a large prospective prebirth cohort study of pregnant women, the Massachusetts General Hospital Obstetric Maternal Study (MOMS), which has been described in detail previously.^{13,14} All women receiving prenatal care at Massachusetts General Hospital or an affiliated health center between 1998 and 2006 were eligible for enrollment. Seventy percent of women approached consented to participate and were enrolled at their first prenatal visit ($n = 9930$); participants were similar to nonparticipants.¹³ Clinical data entered into the EHR at prenatal visits and delivery were used to populate the MOMS database.¹⁵

More recently, we used the Partners HealthCare EHR to obtain clinical data on the children of the MOMS participants, generating a data mart using i2b2 server software (i2b2 v1.6.04, Boston, Mass).¹⁶ The Partners Human Research Committee approved the original study protocol as well as the present analysis.

For the current study, children who were offspring of MOMS participants and who received health care at our institution comprised the analytic cohort. Inclusion criteria were having at least one health care encounter in our EHR after birth but before age 1 year, and at least one health care encounter on or after age 3 years but before age 5 years. A total of 3653 children met these inclusion criteria.

Exposure definition

Severe bronchiolitis was defined as hospital admission before age 1 year for a nonbacterial acute lower respiratory infection, and was extracted from the children's EHR. Children billed for bronchiolitis (International Classification of Diseases, Ninth Revision [ICD-9] 466.xx), respiratory syncytial virus (RSV) (ICD-9 079.6), viral pneumonia (ICD-9 480.x), asthma (ICD-9 493.xx), or wheezing (ICD-9 786.07) from an inpatient location at age less than 1 year were considered to have severe bronchiolitis.¹⁴

Outcome definition

The primary outcome is asthma by age 5 years—defined as ≥ 1 asthma primary diagnosis (ICD-9 493.xx) in the EHR billed on or after age 3 years but before age 5 years, or ≥ 2 asthma medication “events” within a 12-month period of time beginning on or after age 3 years but before age 5 years. “Events” are defined as coded medication entries in the EHR from inpatient and outpatient locations. Asthma medications were obtained from the National Committee for Quality Assurance (NCQA).¹⁷ The NCQA list of medications included asthma controller medications, as well as rescue medications, but did not include oral corticosteroids.

Covariate definitions

We compiled many traditional asthma risk factors. Sex, race/ethnicity, and insurance status at birth were obtained from the child's EHR, as were diagnoses of relevant childhood health outcomes. Data collected include transient tachypnea of the newborn (ICD-9 770.6), atopic dermatitis (AD) (ICD-9 691.8), and dermatitis due to food taken internally (ICD-9 693.1). A diagnosis of AD was made if a child had ≥ 2 billing codes for AD or dermatitis due to food taken internally by age 3 years.

We also examined diagnoses of congenital heart disease (CHD) (ICD-9 745.xx, 746.xx, or 747.xx) and cystic fibrosis (ICD-9 277.0x). A diagnosis of CHD was made if a child had ≥ 3 billing codes for CHD to exclude the possibility that the child received an initial (rule-out) evaluation.¹⁴ Gestational age, birth weight, neonatal intensive care unit (NICU) admission after birth, years of maternal education, maternal smoking during pregnancy, and mode of delivery were obtained from the mothers' charts as part of the original MOMS data collection, or by chart review. Maternal history of asthma was diagnosed if the mother received ≥ 3 billing codes (ICD-9 493.xx) for asthma ever. In cases where information was available in both the child's chart and the MOMS database, information was reviewed for concordance, with clarification by chart review, as needed.

Statistical analyses

All statistical analyses were performed using StataSE 14 (StataCorp., College Station, Tex). Data are presented as proportions with 95% confidence intervals (95% CIs). Unadjusted analyses of the potential risk factors for asthma were conducted using a χ^2 test or Fisher's exact test, as appropriate. All P values were 2-tailed, with $P < .05$ considered statistically significant.

We performed multivariable logistic regression to examine the association of severe bronchiolitis with incident asthma while controlling for confounders, with generalized estimating equations to account for multiple births per mother. Variables were tested for inclusion in the model if they were found to be associated with the outcome in unadjusted analyses ($P < .20$) or were considered clinically relevant by the authors. We also created a logistic regression model to test for the interaction between AD and severe bronchiolitis.

In sensitivity analysis, we excluded asthma (ICD-9 493.xx) as a code for severe bronchiolitis. We also examined the impact of using alternate asthma definitions by substituting different asthma definitions in the same regression model. Results of the regression models are reported as odds ratios (ORs) with 95% CIs.

RESULTS

Our cohort included 3653 children born to 3226 mothers. The cohort was 52% male, 49% white, and 105 infants (2.9%)

TABLE I. Child characteristics of the birth cohort, by asthma outcome (n = 3653)

Child characteristics	Entire cohort (n = 3653)	Asthma by age 5 y		P value
		Yes (n = 421)	No (n = 3232)	
Male sex	1899 (52.0)	262 (62.2)	1637 (50.7)	<.001
Race/ethnicity				.02
White	1771 (48.5)	182 (43.2)	1589 (49.2)	
Black	216 (5.9)	36 (8.6)	180 (5.6)	
Hispanic	466 (12.8)	50 (11.9)	416 (12.9)	
Other	1200 (32.9)	153 (36.3)	1047 (32.4)	
Insurance status*				.07
Private	2044 (56.0)	225 (53.4)	1819 (56.3)	
Public	1498 (41.0)	189 (44.9)	1309 (40.5)	
Other	111 (3.0)	7 (1.7)	104 (3.2)	
Gestational age, wk				<.001
<32	38 (1.0)	15 (3.6)	23 (0.7)	
32-36	262 (7.2)	40 (9.5)	222 (6.9)	
≥37	3353 (91.8)	366 (86.9)	2987 (92.4)	
Birth weight, g				<.001
<2000	77 (2.1)	27 (6.4)	50 (1.6)	
2000-3999	3135 (85.8)	341 (81.0)	2794 (86.5)	
≥4000	441 (12.1)	53 (12.6)	388 (12.0)	
Infant disposition at birth				.005
NICU	179 (4.9)	34 (8.1)	145 (4.5)	
Nursery/NICU triage	2513 (68.8)	283 (67.2)	2230 (69.0)	
Unknown	961 (26.3)	104 (24.7)	857 (26.5)	
Transient tachypnea of the newborn	173 (4.7)	28 (6.7)	145 (4.5)	.049
Congenital heart disease	115 (3.2)	19 (4.5)	96 (3.0)	.09
Cystic fibrosis	59 (1.6)	12 (2.9)	47 (1.5)	.03
Severe bronchiolitis	105 (2.9)	29 (6.9)	76 (2.4)	<.001
Atopic dermatitis before age 3 y	352 (9.6)	69 (16.4)	283 (8.8)	<.001

NICU, Neonatal intensive care unit.

Number (%).

*At birth.

had severe bronchiolitis (Table I). Overall, 421 (11.5%) had asthma by age 5 (Table II). Among the children with severe bronchiolitis in infancy, 29 (27.6%) developed asthma by age 5 years. Among children who did not have severe bronchiolitis in infancy, 392 of 3548 (11.0%) developed asthma.

In unadjusted analyses, we confirmed several known risk factors for childhood asthma, including (black) race, younger gestational age, low birth weight, NICU admission at birth,¹⁸ severe bronchiolitis in infancy, and AD in early childhood (Table I). Maternal risk factors for asthma included cesarean delivery and maternal asthma (Table III). Interestingly, maternal smoking during pregnancy was not significantly associated with age 5-year asthma.

In multivariable logistic regression adjusting for 12 risk factors, severe bronchiolitis remained significantly associated with risk of developing asthma by age 5 years (OR = 2.57, 95% CI 1.61-4.09, $P < .001$). There was no significant interaction between AD and severe bronchiolitis on risk of asthma ($P = .41$). In a sensitivity analysis in which asthma was excluded as a diagnosis code for severe bronchiolitis, there was no significant difference in the association between severe bronchiolitis and age 5-year asthma (Table IV). In sensitivity analyses using alternate definitions of asthma in the same multivariable model, there also were no significant differences in the association between severe bronchiolitis and age 5-year asthma (Table IV).

TABLE II. Qualifying criteria for children who developed asthma by age 5 years

	n (%)
Asthma diagnosis*	
≥1 asthma primary diagnosis	125 (29.7)
≥2 medication "events"	112 (26.6)
≥1 asthma primary diagnosis AND ≥2 medication "events"	184 (43.7)
Asthma medications prescribed†	
Short-acting bronchodilator	263 (88.9)
Inhaled corticosteroid	106 (35.8)
Inhaled corticosteroid/long-acting bronchodilator combination	1 (0.3)
Leukotriene receptor antagonist	20 (6.8)
Other asthma medication	6 (2.0)

*Among 421 children diagnosed with asthma.

†Among 296 children who had ≥2 medication "events" documented between ages 3 and less than 5 years. n reflects children with ≥1 "event" for the specified medication.

DISCUSSION

In this birth cohort of 3653 children in Boston, 105 (2.9%) had severe bronchiolitis in infancy, which is similar to prior studies.^{1,2,14} Asthma between ages 3 and 5 years was diagnosed

TABLE III. Mothers of children in the birth cohort, by asthma outcome (n = 3653)

Maternal characteristics	Entire cohort (n = 3653)	Asthma by age 5 y		P value
		Yes (n = 421)	No (n = 3232)	
Education <12 y	1050 (28.7)	127 (30.2)	923 (28.6)	.49
Smoking during pregnancy				.76
Never smoked or quit smoking	3393 (93.0)	389 (92.6)	3004 (93.0)	
Current smoker	256 (7.0)	31 (7.4)	225 (7.0)	
Mode of delivery				.01
Vaginal	2610 (71.5)	278 (66.0)	2332 (72.2)	
Cesarean section	1043 (28.6)	143 (34.0)	900 (27.9)	
Asthma*	447 (12.3)	90 (21.4)	357 (11.1)	<.001

Number (%).

*n = 3650.

TABLE IV. Sensitivity analyses using a multivariable model of severe bronchiolitis and risk of asthma (n = 3646)

Multivariable model	OR	95% CI	P value
Alternate bronchiolitis definition			
Excluding asthma (ICD-9 493.xx) as a cause of severe bronchiolitis	2.32	1.43-3.77	.001
Alternate asthma definition			
≥1 asthma primary diagnosis	1.88	1.07-3.29	.03
≥1 asthma primary diagnosis or ≥1 annual asthma medication event	2.80	1.83-4.30	<.001

CI, Confidence interval; ICD-9, International Classification of Diseases, Ninth Revision; OR, odds ratio.

in 11.5% of children in this cohort. This rate is concordant with other studies in which asthma prevalence estimates in this age group (0-4 years old) ranged from 3.7% to 23.6%,^{19,20} but the most likely estimate was approximately 10%.¹⁹ Among infants with severe bronchiolitis, 27.6% developed asthma by age 5 years. We observed a significantly higher risk of asthma among those with severe bronchiolitis, even after adjusting for multiple potential confounders. Although the proportion (27.6%) is lower than the more commonly reported 40%-50% prevalence of asthma or recurrent wheezing among children with severe bronchiolitis,^{6,7} it remains high.

Severe bronchiolitis is a risk factor for recurrent early wheezing and childhood asthma.^{6-10,21,22} However, asthma prevalence estimates among this group have been widely disparate, ranging from 20% to 60%. The varying prevalence estimates may be due in part to small sample sizes (n = 47-70) in some prior studies.⁶⁻⁸ Those studies with higher asthma prevalence estimates also examined recurrent wheezing of childhood, with many defining an age cutoff of 2 years^{6,7}; those children may have had transient early wheezing,^{23,24} and not have truly developed asthma. Indeed, in the Tucson Children's Respiratory Study, more than 40% of children with any wheezing in the first 3 years of life and with other asthma risk factors did not go on to develop subsequent asthma.²⁴ Thus, earlier prevalence estimates may not provide an accurate representation of the true prevalence of childhood asthma among children with severe bronchiolitis in infancy.

In studies examining the prevalence of childhood asthma in later childhood (age 6 or 7 years) among children with severe bronchiolitis in infancy, prior studies suggest that 30%-50% developed doctor-diagnosed asthma.^{9,10,22} Reijonen et al⁹ had a case series of

89 children hospitalized for wheezing illness at less than 2 years, and found that 50% had asthma 3 years later. However, this study may have captured early asthma, as they allowed children with any wheezing illness at age less than 2 years into their cohort. In addition, children with clinical bronchiolitis tend to have other features on examination (rales) that were not necessary for inclusion in this cohort. Because this group defined bronchiolitis using wheezing and respiratory distress, it is possible that children may have had other nonbronchiolitis wheezing illnesses. Sigurs et al²¹ reported a lower cumulative prevalence of asthma by age 7 years of 30% among 47 infants previously hospitalized with RSV bronchiolitis in Sweden, compared with only 3% among controls. Their cohort did not include infants with other viral causes of bronchiolitis, which may have affected their outcome. In addition, this Swedish cohort may not be generalizable to the US population with regard to race and/or ethnicity, potentially accounting for the lower prevalence of asthma as compared with the cohort of Castro et al,¹⁰ in which 50% of children with RSV bronchiolitis developed asthma by age 6 years.

In multivariable analysis, we found that severe bronchiolitis in infancy was associated with an OR of 2.57 (95% CI 1.61-4.09) for the development of asthma by age 5 years. Risk estimates for severe bronchiolitis as a cause of childhood asthma vary widely, from OR = 1.58²⁵ to RR = 9.23.²¹ The observed differences across the literature may be due to many factors, including differing definitions of severe bronchiolitis and asthma, the racial and/or ethnic diversity of the population studied, and inclusion of different age groups in the exposure and outcome. Our OR estimate falls within the expected range reported in previous studies.

AD is a known risk factor for asthma, and we previously reported an association between AD and severe bronchiolitis in infancy.¹⁴ Interestingly, we found that there was no interaction between AD and severe bronchiolitis on the outcome of asthma among children in this cohort. Although each remains an individual risk factor, there is no synergistic effect on the outcome of asthma.

One major strength of this study is the large sample size. Our cohort contained data on more than 3600 children in the greater Boston area from birth through age 5 years. Of these children, 105 had been admitted to our institution for severe bronchiolitis in infancy. Many prior studies of severe bronchiolitis and risk of asthma studied fewer children.^{6-8,21} Another strength is our cohort study design. Many variables, such as maternal smoking status, were collected prospectively during pregnancy. Finally, whereas much of the published literature in this field is from Europe,^{6,8,9,21} our cohort is more representative of the US population. Although almost half of our cohort was white, the

remainder comprised a mix of race and ethnicities that may better mirror the US racial/ethnic composition.

There were potential limitations, as well. The use of ICD-9 codes to determine exposure and disease may lead to some misclassification of the outcome. To minimize this risk, a board certified allergist/immunologist (DSB) performed a chart review of a subset of those with the outcome of asthma, and confirmed that 92% truly had asthma. Another potential limitation is the baseline characteristics of our cohort. Although we may have seen a higher prevalence of asthma overall if our cohort was more diverse, the demographic characteristics of this population are still more likely to reflect those of a US cohort. Our study lacked viral testing data during the initial hospitalization for bronchiolitis. Rhinovirus bronchiolitis in infancy has been shown to predict recurrent wheezing at age 3 years,²⁶ and it would have been interesting to examine the asthma risk of specific viral causes of bronchiolitis. In addition, because most of our data were extracted from the medical records, we were not able to assess several exposures during early childhood, such as food allergy or use of certain medications (eg, acetaminophen). However, we were able to assess certain comorbidities, such as AD, as well as respiratory and cardiac diseases, that may have significantly affected the outcome. Finally, although asthma may have been diagnosed by age 5 years, it is possible that asthma or recurrent wheezing was outgrown by adolescence, as in the Tucson Children's Respiratory Study.^{24,27}

In summary, in this infant birth cohort, we found that the rates of severe bronchiolitis in infancy and asthma by age 5 years were concordant with previously published data. Although we confirmed that infants with severe bronchiolitis have an increased prevalence of asthma by age 5 years, this was slightly lower than in previously published studies, highlighting the significance of this large, diverse cohort. In addition, the lower prevalence of asthma in this group may also allay the fears of some families who worry about their child's increased risk of asthma after bronchiolitis hospitalization. These results underscore the importance of identifying those children with severe bronchiolitis who are most at risk of developing asthma to target interventions in that group. We plan to examine these issues in our ongoing multicenter cohort study of 921 infants with severe bronchiolitis.²⁸ Specifically, our prospective cohort will combine clinical and laboratory data to create a childhood wheezing index to identify children with severe bronchiolitis who are at higher risk of developing recurrent wheezing and childhood asthma.^{29,30}

Acknowledgments

We would like to thank Janice Espinola, MPH, for her help with the statistical methods.

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