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The Severity-Dependent Relationship of Infant Bronchiolitis on the Risk and Morbidity of Early Childhood Asthma

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Abstract

Background—Infants hospitalized for bronchiolitis have a high rate of early childhood asthma. It is not known whether bronchiolitis severity correlates with the risk of early childhood asthma or with asthma-specific morbidity.

Objectives—To determine whether a dose-response relationship exists between severity of infant bronchiolitis and both the odds of developing early childhood asthma and asthma-specific morbidity.

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Key Messages

- There is a dose-response relationship between severity of infant bronchiolitis, as determined by most advanced level of healthcare, and the development of early childhood asthma.
- In addition to increased asthma prevalence, severity of bronchiolitis positively correlates with early childhood asthma morbidity.
- The phenotype of asthma following infant bronchiolitis accounts for nearly one-third of early childhood asthma diagnoses.

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Methods—We conducted a population-based retrospective birth cohort study of term, healthy infants born 1995-2000 and enrolled in a statewide Medicaid program. We defined bronchiolitis severity by categorizing infants into mutually exclusive groups based on most advanced level of healthcare for bronchiolitis. Healthcare visits, asthma-specific medications, and demographics were identified entirely from Medicaid and linked vital records files. Asthma was ascertained between 4-5.5 years, and one-year asthma morbidity (hospitalization, emergency department visit, or oral corticosteroid course) was determined between 4.5-5.5 years, among children with prevalent asthma.

Results—Among 90,341 children, 18% had an infant bronchiolitis visit, and these infants contributed to 31% of early childhood asthma diagnoses. Relative to children with no infant bronchiolitis visit, the adjusted odds ratios for asthma were 1.86 [95% confidence intervals 1.74-1.99], 2.41 (2.21-2.62) and 2.82 (2.61-3.03) in the Outpatient, Emergency Department, and Hospitalization groups respectively. Children hospitalized with bronchiolitis during infancy had increased early childhood asthma morbidity compared with children with no bronchiolitis visit.

Conclusion—To our knowledge, this is the first study to demonstrate the dose-response relationship between severity of infant bronchiolitis and the increased odds of both developing early childhood asthma and experiencing asthma-specific morbidity.

Keywords

Bronchiolitis; asthma

Introduction

Asthma is one of the most common chronic conditions of childhood and accounts for significant morbidity.¹ The etiology and morbidity of asthma is thought to be due to a number of modifiable and non-modifiable factors, including family history, genetic predisposition, and environmental exposures such as viral infections.²⁻⁴ Viral bronchiolitis results in significant morbidity, affecting 20% of infants annually.^{5,6} Furthermore, up to 3% of healthy infants in the United States are hospitalized for bronchiolitis, resulting in an estimated 120,000 hospitalizations annually and bronchiolitis rates are increasing.⁷ Morbidity is high not only related to the infant bronchiolitis episode, but a high rate of asthma within the first decade of life, has been observed following severe bronchiolitis during infancy.⁸⁻¹⁰ Although, observational studies have reported that over 30% of infants hospitalized with bronchiolitis subsequently develop asthma, the relationship between the infant bronchiolitis episode and later asthma is not completely understood, since the majority of infants with bronchiolitis do not develop asthma.¹¹

Several seminal observational studies have tracked childhood asthma outcomes among children with a history of a bronchiolitis hospitalization during infancy and a non-hospitalized comparison group.^{8,9,11-17} However, asthma outcomes for outpatient infant bronchiolitis events in the non-hospitalized groups were not reported, thus the relationship between infant bronchiolitis severity and subsequent risk or morbidity of asthma is not known from these investigations. A limited number of prospective birth cohorts, including two with children at high-risk for asthma, have also contributed to our understanding of asthma risk among children with a history of bronchiolitis or wheezing lower respiratory tract illness in the first years of life.^{6,10,18-21} However, the wheezing illnesses identified within these cohorts were primarily outpatient events, and the risk or morbidity of asthma associated with infant bronchiolitis requiring emergency department visits or hospitalizations were both infrequent and not reported. Therefore, despite several longitudinal investigations focused on the role of viral infections in asthma inception, it is not known whether there is a severity-dependent relationship between severity of infant bronchiolitis and both the risk and morbidity of early childhood asthma. Nor is it known, at a population-based level, what proportion of children

with asthma had clinically significant bronchiolitis as infants, or if a familial predisposition to develop asthma modifies the risk of developing asthma after infant bronchiolitis.

To answer these questions, we utilized our population-based retrospective birth cohort of over 90,000 term, non-low birth weight, otherwise healthy children in the Tennessee Asthma Bronchiolitis Study (TABS) constructed from healthcare visits, asthma-specific medications, and demographics identified from Medicaid claims, pharmacy data, and linked vital records files. We hypothesized that severity of clinically significant bronchiolitis, including both outpatient and inpatient healthcare, would be positively correlated with both an increased odds of developing early childhood asthma and increased asthma-specific morbidity among children with prevalent disease. Lastly, in a subset of mother-infant dyads in whom maternal history could be determined, we investigated how maternal asthma modified the association between bronchiolitis and early childhood asthma inception.

Methods

Study design and population

To estimate the association of bronchiolitis during infancy with the development of early childhood asthma, we conducted a population-based retrospective birth cohort study of over 90,000 term, non-low birth weight infants enrolled in TennCare within the first month of life, 1995- 2000, the Tennessee Asthma Bronchiolitis Study (TABS). Only children born between 1995 and 2000 were included, as all children were followed to 5.5 years using the years for which data were available. In 1994, TennCare replaced the federal Medicaid program, as a state-based managed health care program that covered Medicaid-eligible individuals and the uninsured.²² TennCare provides health insurance for approximately 50% of infants born in Tennessee. Data were obtained from linked TennCare administrative data files and Tennessee State vital records files using previously described methods at our study institution.^{23,24} Analysis files contained no personal identifiers and study results are reported in aggregate and cannot be linked to individuals. The protocol was approved by the Institutional Review Board of Vanderbilt University and reviewed and approved by representatives of the Tennessee Department of Health and the Bureau of TennCare.

Eligible children were continuously enrolled in TennCare during the first year of life, during which healthcare visits for bronchiolitis were captured, and between 3.5-5.5 years during which early childhood asthma was defined. Continuous enrollment was considered no more than 21 days of non-enrollment during the first 12 months of life and no more than 60 days of non-enrollment between 3.5-5.5 years. In order to investigate the association of bronchiolitis during infancy and subsequent asthma without the potential confounding of low birth weight or chronic disease, this investigation included only term (estimated gestational age [EGA] ≥ 37 weeks), non-low birth weight (≥ 2500 grams), otherwise healthy infants. We determined EGA in weeks by date of last menstrual period on the birth certificate (87%), or imputed based on median gestational period in weeks for the infant's race, birth weight, and birth year (13%).²⁵ We excluded infants with any of the following before 3.5 years (4.6%): Current Procedural Terminology (CPT) code indicating surgery for congenital heart disease, receipt of RSV immunoprophylaxis, or International Classification of Diseases, Ninth Revision (ICD-9) code indicating congenital heart disease, chronic lung disease (bronchopulmonary dysplasia), congenital anomaly of the upper airway, upper alimentary tract atresia or stenosis, neurologic disorder, immunodeficiency, cystic fibrosis, diabetes mellitus, renal disease, or cancer.

Predictor variables

We identified health care visits for bronchiolitis during the first 12 months of life using ICD-9 codes for bronchiolitis (466.1) and/or RSV pneumonia (480.1). ICD-9 diagnoses of

bronchiolitis in infants have been validated using models to correlate with RSV circulation.²⁶ Clinically significant bronchiolitis was defined as a healthcare visit for bronchiolitis. Bronchiolitis severity was defined by categorizing children into mutually exclusive groups based on their most advanced level of healthcare (hospitalization, 23 hour observation, emergency department (ED) visit, or clinic visit with ICD-9 codes for bronchiolitis). Hospitalizations and 23 hour observations were combined into the *Hospitalization* group. Infants without any bronchiolitis visits were categorized into the *No Visit* group.

Other demographic and baseline characteristics were determined from birth certificate data and TennCare files. Infant race/ethnicity (mutually exclusive categories of white, black, Hispanic, other/unknown) and region of residence (urban, suburban, or rural) were identified from TennCare enrollment files. Demographic variables determined from birth certificate data included: birth weight, gender, siblings (none, one, two or more based on report of number of prior live births), maternal age at delivery, maternal education level, quantified maternal smoking during pregnancy, and marital status.

We utilized maternal asthma, one measure of familial predisposition to develop asthma, to evaluate whether maternal asthma modified the association between bronchiolitis during infancy and subsequent asthma development. Maternal asthma was ascertained in the nested subgroup of mother-infant dyads who met the following criteria: infants were term, otherwise healthy and mothers were continuously enrolled in TennCare from 180 days prior to pregnancy through delivery. Maternal continuous enrollment included no more than 45 days of non-enrollment during 180 days prior to pregnancy through delivery. Maternal asthma was similarly determined using health care encounter and/or pharmacy file claims using a previously validated method of identifying individuals with asthma.²⁵

Outcome variables

The main outcome was diagnosis of early childhood asthma between 4 to 5.5 years among the population-based cohort of 90,341 children. We used a 1.5 year ascertainment period to capture children with milder disease who may seek treatment only as needed or during well child visits. We studied asthma diagnoses after 4 years to exclude “transient early wheezers” who wheeze with viral infections during the first years of life.⁴ Early childhood asthma was determined using health care encounter and/or pharmacy file claims employing similar algorithms used for both epidemiology and outcomes research.^{27,28} Children with an ICD-9 diagnosis code of 493 (asthma) in any of the discharge diagnosis fields for inpatient, other hospital care (23 hour observation), or emergency department visit or 2 outpatient physician visit claims were considered to have asthma. In addition, children with two prescriptions for any short-acting beta-agonist within a 12 month period or a prescription for other asthma medications (including inhaled corticosteroids and long-acting beta agonists) were considered to have early childhood asthma.

We also assessed the relationship between bronchiolitis severity during infancy and one-year asthma morbidity among children with prevalent disease by 4.5 years. For this analysis we required children to meet the definition of asthma between 3.5-4.5 years, and have a full one-year of follow-up from 4.5-5.5 years during which the morbidity of their asthma was determined. One-year asthma morbidity was defined between ages 4.5-5.5 years as an asthma hospitalization, emergency department visit, and/or course of systemic corticosteroids among children with prevalent asthma diagnosed between 3.5 to 4.5 years.

Statistical analysis

The main predictor variable for each analysis was severity of bronchiolitis during infancy defined by type of bronchiolitis healthcare visit. The main outcome variables were: (1) early

childhood asthma ascertained between 4-5.5 years for analysis of the relationship between infant bronchiolitis severity and asthma diagnosis, and (2) one-year asthma morbidity ascertained between 4.5-5.5 years in children with prevalent disease between 3.5-4.5 years for analysis of the relationship of infant bronchiolitis severity with early childhood asthma morbidity. We compared the proportion of children with asthma by the predictor variables using chi-square statistics. Multivariable logistic regression models were used to measure the relative adjusted odds of asthma during early childhood associated with infant bronchiolitis severity.²⁹ The statistical models were adjusted for birth weight, gender, infant race/ethnicity, maternal smoking during pregnancy, maternal education level, region of residence, and other living siblings. We also determined the risk of early childhood asthma in children with a history of no infant bronchiolitis visit, one, or two or more bronchiolitis episodes. Distinct bronchiolitis episodes were new ICD diagnoses separated by at least 4 weeks. A multivariable logistic regression model was also applied to assess the joint effect of maternal asthma and bronchiolitis severity on odds of early childhood asthma by including a cross-product in the model. In stratified analyses, we determined whether history of maternal asthma or other baseline and demographic characteristics modified the relationship between bronchiolitis and early childhood asthma. Lastly, we assessed the adjusted relative odds of one-year asthma morbidity between 4.5 to 5.5 years in the subset of children diagnosed with asthma between 3.5-4.5 years. Analyses were conducted using SAS version 9.1 (SAS Institute Cary, NC) and R version 2.6.1.

Results

A total of 90,341 term healthy children were included in the cohort. Forty-nine percent of the children were female; the children were white (56%), black (39%), and Hispanic (2%), (see Table I). The median EGA was 40 weeks and median birth weight was 3289 grams. Overall, 26% of children had mothers who smoked during pregnancy. Eighteen percent of children had at least one healthcare visit for bronchiolitis during infancy and children were classified into the following groups: *No Visit* (82%), *Outpatient* (9%), *ED* (4%), or *Hospitalization* (5%). In total, 11% were diagnosed with asthma between 4 to 5.5 years. The 18% of children with clinically significant bronchiolitis during infancy accounted for 31% of children with early childhood asthma.

The proportions of children with early childhood asthma by severity of infant bronchiolitis were: *No Visit* (9%), *Outpatient* (16%), *ED* (19%) and *Hospitalization* (22%), ($p < 0.001$), (see Table II). Relative to children without a bronchiolitis visit during infancy (*No Visit*), the odds ratios for asthma between 4 to 5.5 years were 1.86 [95% confidence intervals (CI) 1.74-1.99], 2.41 (95% CI 2.21-2.62) and 2.82 (95% CI 2.61-3.03) in the *Outpatient*, *ED*, and *Hospitalization* groups respectively, adjusted for birth weight, gender, race, maternal smoking during pregnancy, maternal age at delivery, maternal education level, region of residence, and other living siblings at birth. Overall, 15% of children had a single bronchiolitis episode during infancy and 3% had 2 or more episodes. Compared to children with no ICD-9 diagnosis of bronchiolitis during infancy, the adjusted ORs for early childhood asthma were 2.01 (95% CI 1.91-2.12) and 3.33 (95% CI 3.09-3.66) for those with one and two or more bronchiolitis episodes, respectively.

From the cohort of 90,341 children, a nested subset of 51,669 who had mothers with available history and met continuous enrollment criteria were studied to investigate the odds of early childhood asthma with bronchiolitis during infancy in models stratified by maternal asthma. Seven percent of mothers (3,827/51,669) met the definition for asthma. When adjusted for having a mother with asthma, the relationship between bronchiolitis severity during infancy and early childhood asthma was similar when comparing the entire cohort to the children with maternal asthma identified from the nested subset (see Figure 1). There was no statistically

significant interaction by maternal asthma on the relationship between bronchiolitis severity during infancy and early childhood asthma ($p=0.29$).

Although the risk of early childhood asthma was higher in children with a history of maternal asthma, the patterns of early childhood asthma risk associated with severity of bronchiolitis during infancy were similar in the children with maternal asthma and without maternal asthma. Among children whose mothers had asthma, the adjusted odds ratios for asthma between 4 to 5.5 years were 1.85 (95% CI 1.43-2.38), 2.46 (95% CI 1.84-3.29) and 2.25 (95% CI 1.73-2.94) in the *Outpatient*, *ED*, and *Hospitalization* groups respectively. Similarly, among children whose mothers did not have asthma, the analogous odds ratios were 1.84 (95% CI 1.68-2.02), 2.53 (95% CI 2.26-2.83) and 2.86 (95% CI 2.58-3.16) in the *Outpatient*, *ED*, and *Hospitalization* groups respectively. Due to the combined effects of independent variables maternal asthma and bronchiolitis during infancy, the relative odds of early childhood asthma increased with severity of infant bronchiolitis and was greatest in those with a history of maternal asthma. Among children with both a maternal history of asthma and an infant hospitalization for bronchiolitis the odds of early childhood asthma was 4.18 times that of children without either risk factor (data not shown).

We also evaluated whether the severity of bronchiolitis during infancy and early childhood asthma varied by other demographic and baseline characteristics (See Table E1 Online Repository). In general, the same dose response relationship with bronchiolitis severity was seen for all characteristics assessed. In particular, increased odds of childhood asthma were observed for children who at birth had a mother who did not smoke during pregnancy, had one or more siblings, were black, or lived in an urban region of the state compared to their respective counterparts.

Next we investigated the association between severity of bronchiolitis during infancy and early childhood asthma morbidity. Among the 7,607 cohort children meeting our definition of asthma between 3.5-4.5 years, 1,455 (19%) met criteria for an asthma-specific morbidity event, as defined by at least one asthma hospitalization, ED visit, or prescription filled for oral corticosteroids, during the follow-up year from 4.5-5.5 years. We characterized these 7,607 children according to their infant bronchiolitis history and determined the odds of having an asthma-specific morbidity event between 4.5-5.5 years as 18%, 17%, 22%, and 24% in the *No Visit*, *Outpatient*, *ED*, and *Hospitalization* groups respectively ($p<0.001$), Table II. Compared to the *No visit* group, the adjusted odds ratios of having an asthma-specific event were 0.95 (95% CI 0.80-1.14) in the *Outpatient*, 1.12 (95% CI 0.91-1.38) in the *ED*, and 1.51 (1.26-1.80) in the *Hospitalization* groups (Figure 3).

Discussion

While the association of viral lower respiratory tract infection during infancy and subsequent childhood wheezing is well established, this study addresses important gaps in our knowledge regarding the relationship of bronchiolitis severity on early childhood asthma risk and asthma morbidity. To our knowledge, this is the first study to demonstrate the dose-response relationship between the severity of infant bronchiolitis and the increased odds of both developing early childhood asthma and experiencing increased asthma-specific morbidity, as well as establishing that the phenotype of asthma following infant bronchiolitis in a population-based sample of low-risk infants accounts for nearly one-third of early childhood asthma.

We also investigated whether a familial predisposition to asthma, as measured by having a mother with asthma, modified the association between infant bronchiolitis and early childhood asthma. As expected, a greater proportion of children with a mother who had asthma developed early childhood asthma compared with children whose mothers did not have asthma. There

was no interaction between familial predisposition to develop asthma and severity of infant bronchiolitis on the odds of early childhood asthma. The odds of asthma increased with increasing severity of infant bronchiolitis in children with and without a maternal history. However, because of the joint effects, the absolute odds of asthma in patients with infant bronchiolitis was appreciably greater in children with a maternal history of asthma.

It is not known whether children who develop bronchiolitis during infancy also have an intrinsic predisposition to develop early childhood asthma or if respiratory viruses that infect the infant host play a role in the development of subsequent recurrent wheezing or asthma.^{2,30-32} The dose response relationship of bronchiolitis severity on odds of early childhood asthma demonstrated in this current study, which is not modified by a familial predisposition to develop asthma, could reflect either the magnitude of lung injury and impairment in lung development following infection, or an alteration in host immune development. Although findings from animal models lend some credence to these hypotheses, evidence from human studies is limited and conflicting.^{2,30-35} Recent experimental investigations provide possible mechanistic insight into the role of viral respiratory tract infections in the development of chronic lung inflammation and the augmentation of allergic airway inflammation.^{31,36} These effects are likely to be more pronounced in individuals who have a genetic susceptibility to asthma.³⁷ As RSV-IgE responses have been shown to positively correlate with increased frequency of subsequent recurrent wheeze, this may partly explain why bronchiolitis severity is positively associated with increased early childhood diagnosis, although this has not been replicated.³⁸ Evidence from a non-randomized investigation of RSV immunoprophylaxis supports the hypothesis that modification of RSV severity in premature infants decreases the risk of subsequent recurrent wheezing.³⁹ Randomized longitudinal investigations aimed at modifying or preventing viral infection will ultimately clarify the association between viruses and the development of early childhood asthma, with potential implications for asthma prevention.

There are several limitations of this work. In this retrospective cohort study using existing data to categorize study variables, misclassification of the predictor variables is possible. For example, there may be infants in the *No Visit* group who had bronchiolitis but did not have a healthcare visit. This misclassification would bias results toward the null. Hospitalization for bronchiolitis has been used as a measure of severity for decades, however it is possible that social factors and infant age influenced providers' decisions to hospitalize. Maternal asthma was the only marker of a genetic predisposition to development of asthma used. Therefore in the group of infants without maternal asthma, there are likely infants with an unmeasured familial predisposition to develop asthma. Although bronchiolitis diagnoses were not confirmed, we used ICD-9 diagnoses, a method which captures objective physician characterized outcomes at the time of illness that would not be influenced by recall bias. In addition, the overall bronchiolitis incidence of 18% is consistent with previously published reports.^{5,6} We defined asthma outcomes using ICD-9 diagnoses and medication use and may not detect asymptomatic or undiagnosed individuals, or individuals who have not sought treatment.⁴⁰ Historical and emerging data demonstrate the increased risk of recurrent wheezing or asthma following both RSV bronchiolitis and non-RSV bronchiolitis, caused by viruses such as rhinovirus.^{8-11,15,17,18,21,41} We did not capture the etiology of bronchiolitis, however in our previous studies we demonstrated that 80% of visits for bronchiolitis during infancy in the TABS cohort occurred during winter virus season between November and April.⁴² Therefore findings from this current investigation likely reflect early childhood asthma outcomes predominately, but not exclusively, associated with RSV bronchiolitis during infancy. While it is established that RSV lower respiratory tract infection in the first years of life is associated with increased risk of recurrent wheeze or asthma at age 6 years, there is conflicting data about whether this association persists into adolescence.⁹⁻¹¹ However, the burden of early childhood asthma even in the 5th and 6th years of life is associated with substantial patient morbidity and health care use. Therefore delineating the relationship of

environmental factors, such as viral bronchiolitis during infancy, to the subsequent development and morbidity of early childhood asthma is important in disease and morbidity prevention efforts. Whether our results are generalizable to other populations is not known. We conducted our study in the Medicaid population in which approximately half of infants born in Tennessee are enrolled. It is likely that the relationship between bronchiolitis and early childhood asthma would be similar in non-Medicaid populations.

Conclusions

Increased severity of infant bronchiolitis is associated with both an increased odds of early childhood asthma in a severity-dependent manner, and increased asthma-specific morbidity during early childhood. The phenotype of early childhood asthma following infant bronchiolitis accounts for nearly one-third of early childhood asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma--United States, 1980-2004. *MMWR Surveill Summ* 2007;56:1-54. [PubMed: 17947969]
2. Gern JE, Rosenthal LA, Sorkness RL, Lemanske RF Jr. Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol* 2005;115:668-74. [PubMed: 15805982]
3. Chan-Yeung M, Ferguson A, Watson W, mich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116:49-55. [PubMed: 15990772]
4. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8. [PubMed: 7800004]
5. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child* 1986;140:543-6. [PubMed: 3706232]
6. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study. II. Lower respiratory tract illness in the first year of life. *Am J Epidemiol* 1989;129:1232-46. [PubMed: 2729259]
7. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA* 1999;282:1440-6. [PubMed: 10535434]
8. Noble V, Murray M, Webb MS, Alexander J, Swarbrick AS, Milner AD. Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child* 1997;76:315-9. [PubMed: 9166022]
9. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;171:137-41. [PubMed: 15516534]

10. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–5. [PubMed: 10470697]
11. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161:1501–7. [PubMed: 10806145]
12. Murray M, Webb MS, O'Callaghan C, Swarbrick AS, Milner AD. Respiratory status and allergy after bronchiolitis. *Arch Dis Child* 1992;67:482–7. [PubMed: 1580676]
13. Kotaniemi-Syrjnen A, Laatikainen A, Waris M, Reijonen TM, Vainionp R, Korppi M. Respiratory syncytial virus infection in children hospitalized for wheezing: virus-specific studies from infancy to preschool years. *Acta Paediatr* 2005;94:159–65. [PubMed: 15981748]
14. Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. *Arch Pediatr Adolesc Med* 2004;158:1070–6. [PubMed: 15520345]
15. Fjerli HO, Farstad T, Rod G, Ufert GK, Gulbrandsen P, Nakstad B. Acute bronchiolitis in infancy as risk factor for wheezing and reduced pulmonary function by seven years in Akershus County, Norway. *BMC Pediatr* 2005;5:31. [PubMed: 16109158]
16. Bradley JP, Bacharier LB, Bonfiglio J, Schechtman KB, Strunk R, Storch G, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. *Pediatrics* 2005;115:e7–14. [PubMed: 15629968]
17. Henderson J, Hilliard TN, Sherriff A, Stalker D, Shammari NA, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: A longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005;16:386–92. [PubMed: 16101930]
18. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005;116:571–7. [PubMed: 16159626]
19. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178:667–72. [PubMed: 18565953]
20. Kusel MM, de Klerk NH, Holt PG, Keadze T, Johnston SL, Sly PD. Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *Pediatr Infect Dis J* 2006;25:680–6. [PubMed: 16874165]
21. Kusel MM, de Klerk NH, Keadze T, Vohma V, Holt PG, Johnston SL, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007;119:1105–10. [PubMed: 17353039]
22. Mirvis DM, Chang CF, Hall CJ, Zaar GT, Applegate WB. TennCare--health system reform for Tennessee. *JAMA* 1995;274:1235–41. [PubMed: 7563515]
23. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998;148:1094–102. [PubMed: 9850132]
24. Piper JM, Ray WA, Griffin MR, Fought R, Daugherty JR, Mitchel E Jr. Methodological issues in evaluating expanded Medicaid coverage for pregnant women. *Am J Epidemiol* 1990;132:561–71. [PubMed: 2202203]
25. Hartert TV, Neuzil KM, Shintani AK, Mitchel EF Jr, Snowden MS, Wood LB, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *Am J Obstet Gynecol* 2003;189:1705–12. [PubMed: 14710102]
26. Schanzer DL, Langley JM, Tam TW. Hospitalization attributable to influenza and other viral respiratory illnesses in Canadian children. *Pediatr Infect Dis J* 2006;25:795–800. [PubMed: 16940836]
27. Wakefield DB, Cloutier MM. Modifications to HEDIS and CSTE algorithms improve case recognition of pediatric asthma. *Pediatr Pulmonol* 2006;41:962–71. [PubMed: 16871628]
28. Dombkowski KJ, Leung SW, Gurney JG. Prematurity as a predictor of childhood asthma among low-income children. *Ann Epidemiol* 2008;18:290–7. [PubMed: 18291674]

29. Dupont, WD. Statistical Modeling for Biomedical Researchers. Cambridge: Cambridge University Press; 2002. Multiple Logistic Regression; p. 143-202.
30. Openshaw PJ, Yamaguchi Y, Tregoning JS. Childhood infections, the developing immune system, and the origins of asthma. *J Allergy Clin Immunol* 2004;114:1275–7. [PubMed: 15577822]
31. Kim EY, Battaile JT, Patel AC, You Y, Agapov E, Grayson MH, et al. Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. *Nat Med* 2008;14:633–40. [PubMed: 18488036]
32. Legg JP, Hussain IR, Warner JA, Johnston SL, Warner JO. Type 1 and type 2 cytokine imbalance in acute respiratory syncytial virus bronchiolitis. *Am J Respir Crit Care Med* 2003;168:633–9. [PubMed: 12773328]
33. Singh AM, Moore PE, Gern JE, Lemanske RF Jr, Hartert TV. Bronchiolitis to asthma: a review and call for studies of gene-virus interactions in asthma causation. *Am J Respir Crit Care Med* 2007;175:108–19. [PubMed: 17053206]
34. Renzi PM, Turgeon JP, Marcotte JE, Drblik SP, Berube D, Gagnon MF, et al. Reduced interferon-gamma production in infants with bronchiolitis and asthma. *Am J Respir Crit Care Med* 1999;159:1417–22. [PubMed: 10228104]
35. van Schaik SM, Tristram DA, Nagpal IS, Hintz KM, Welliver RC, Welliver RC. Increased production of IFN-gamma and cysteinyl leukotrienes in virus-induced wheezing. *J Allergy Clin Immunol* 1999;103:630–6. [PubMed: 10200012]
36. Bartlett NW, Walton RP, Edwards MR, Aniscenko J, Caramori G, Zhu J, et al. Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. *Nat Med* 2008;14:199–204. [PubMed: 18246079]
37. Koraka P, Murgue B, Deparis X, Setiati TE, Suharti C, van Gorp EC, et al. Elevated levels of total and dengue virus-specific immunoglobulin E in patients with varying disease severity. *J Med Virol* 2003;70:91–8. [PubMed: 12629649]
38. Welliver RC, Sun M, Rinaldo D, Ogra PL. Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. *J Pediatr* 1986;109:776–80. [PubMed: 3772657]
39. Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr* 2007;151:34–42. [PubMed: 17586188]
40. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40–7. [PubMed: 15241342]
41. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy--the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111:66–71. [PubMed: 12532098]
42. Carroll K, Gebratsadik T, Griffin M, Wu P, Dupont W, Mitchel E, et al. The increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state healthcare insurance plan. *Pediatrics* 2008;122:58–64. [PubMed: 18595987]

Abbreviations used

RSV	respiratory syncytial virus
TABS	Tennessee Asthma Bronchiolitis Study
EGA	estimated gestational age
CPT	Current Procedural Terminology

ICD-9

International Classification of Diseases, Ninth Revision

ED

emergency department

95% CI

95% Confidence interval

Infant Bronchiolitis Severity	No Visit (Reference)		Outpatient		ED		Hospitalization	
Number of Infants								
	■	●	■	●	■	●	■	●
Infants with asthma	6,780	454	1,274	102	743	78	1,056	97
Total infants	73,940	2,860	7,858	386	3,825	253	4,718	328

Figure 1.

Odds Ratios and Proportions of Early Childhood Asthma by Bronchiolitis Severity During Infancy, Among Children Enrolled in Tennessee Medicaid 1995-2000 and Among Children with Maternal Asthma Identified from Subset with Mothers Continuously Enrolled in Tennessee Medicaid.

* As identified from subset of 51,669 mother-infant dyads in which mothers were continuously enrolled in Tennessee Medicaid

(%) denotes the proportion of children in each category diagnosed with asthma (numerator/denominator)

Table I
Infant and Maternal Characteristics by Infant Bronchiolitis Severity among Children Enrolled in Tennessee Medicaid, 1995-2000

Characteristic	All		No visit for bronchiolitis		Bronchiolitis clinic visit		Bronchiolitis emergency department visit		Bronchiolitis hospitalization	
	n	%	n	%	n	%	n	%	n	%
Median birth weight, grams [IQR]*	N=90,341 3289 [3005-3600]		N=73,940 3289 [3005-3600]		N=7,858 3289 [3005-3629]		N=3,825 3260 [2977-3572]		N=4,718 3260 [2977-3572]	
Median EGA[†], weeks [IQR]	40 [39-40]		40 [39-40]		39 [39-40]		39 [39-40]		39 [39-40]	
Maternal age[‡], years Median [IQR] (N=90,170)	22 [19-26]		22 [19-26]		22 [19-25]		21 [19-25]		21 [19-25]	
Infant gender										
Male	46,329	51	36,845	50	4,519	58	2,241	59	2,724	58
Female	44,012	49	37,098	50	3,339	42	1,584	41	1,994	42
Infant race										
White	50,269	56	39,938	54	5,270	67	1,790	47	3,271	69
Black	34,919	39	29,696	40	2,214	28	1,839	48	1,170	25
Hispanic	2041	2	1,779	2	121	2	60	2	81	2
Other/Unknown	3,112	3	2,527	3	253	3	136	4	196	4
Maternal education (N=90,174)										
<12 Years	39,597	44	31,939	43	3,357	43	1,882	49	2,329	49
12 Years	39,832	44	32,752	44	3,537	45	1,595	42	1,948	41
>12 Years	10,835	12	9,100	12	953	12	345	9	437	9
Maternal asthma[§] (N=51,669)										
No	47,842	93	38,879	93	4095	91	2275	90	2593	89
Yes	3,827	7	2860	7	386	9	253	10	328	11
Maternal age, years (N=90,170)										
15-19	26782	30	21,993	30	2,213	28	1,184	31	1,392	30
20-29	51773	57	41,905	57	4,712	60	2,269	59	2,887	61
30-44	10929	12	9,323	13	869	11	335	9	402	9
Maternal smoking (N=90,106)										

Characteristic	All	No visit for bronchiolitis	Bronchiolitis clinic visit	Bronchiolitis emergency department visit	Bronchiolitis hospitalization
	N=90,341	N=73,940	N=7,858	N=3,825	N=4,718
Non-smoker	66,492	55,308	5,433	2,741	3,010
Smoker	23,614	18,436	2,403	1,078	1,697
Number of siblings (N=90,268)					
No Siblings	37,028	30,839	3,113	1,420	1,656
One sibling	27,969	22,448	2,663	1,211	1,647
Two or more siblings	25,271	20,592	2,072	1,193	1,414
Region of residence (N=90,267)					
Urban	39,204	33,013	2,601	2,249	1,341
Suburban	20,720	16,838	2,136	713	1,033
Rural	30,343	24,025	3,115	863	2,340

* interquartile range

† estimated gestational age

maternal age at delivery

§ subset includes children whose mothers were continuously enrolled in Tennessee Medicaid 180 days prior to pregnancy through delivery allowing for determination of maternal asthma history

// maternal smoking during pregnancy

Table II**Relative Odds of an Asthma-specific Morbidity Event* by Infant Bronchiolitis Severity among Children Enrolled in Tennessee Medicaid, 1995-2005**

Children diagnosed with asthma between 3.5 to <4.5 years (N=7,607)				
Infant Bronchiolitis Severity Group	Number of subjects	Asthma Morbidity* (age 4.5 to 5.5 years)		Adjusted [†] OR (95% CI)
		cases	%	
No Visit for bronchiolitis	5063	931	18	1
Bronchiolitis clinic visit	1039	176	17	0.95 (0.80-1.14)
Bronchiolitis emergency department visit	622	139	22	1.12 (0.91-1.38)
Bronchiolitis hospitalization	883	209	24	1.51 (1.26-1.80)

* Hospitalization, emergency department visit, or course of oral corticosteroids

[†] Adjusted for infant birth weight, infant gender, infant race/ethnicity, maternal smoking during pregnancy, maternal education level, region of residence in the state, and other living siblings. Less than 1% were excluded from multivariable analyses due to missing covariates or region of residence.