Published in final edited form as:

Paediatr Perinat Epidemiol. 2014 November ; 28(6): 521–526. doi:10.1111/ppe.12150.

Gestational age-specific associations between infantile acute bronchiolitis and asthma after age five

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Abstract

Background—Infantile acute bronchiolitis is a risk factor for the development of pediatric asthma. The associations might differ according to gestational age.

Methods—Datasets of emergency department (ED) visits (Jan 2002 to June 2010) and live birth records (Jan 2002 to Dec 2004) from the state of Georgia were linked for all children who survived one year. Exposure was an ED visit for acute bronchiolitis during infancy (AB), and the outcome was an ED visit for asthma after age five years. The risk of asthma among children with AB ($n = 11,564$) was compared with the risk of asthma among children who did not have an ED visit for AB but who utilized the ED for another reason during infancy ($n = 131,694$). Associations were estimated using log-binomial regression models that controlled for several plausible confounders. Effect measure modification of the risk ratio by gestational age was investigated.

Results—Crude asthma risks (per 100 children) through June 2010 were 4.5 for children with AB and 2.3 for children without AB. The adjusted risk ratio for the overall association was 1.89 (95% confidence interval (CI) 1.73, 2.108). We did not observe effect modification of the risk ratio by gestational age.

Conclusion—A positive association was observed between ED visits for AB and subsequent asthma ED visits after age five; associations did not vary meaningfully by gestational age. Sensitivity analyses did not suggest large biases due to differences in ED utilization across socio-demographic groups or loss to follow-up from residential migration.

Asthma is a complex disease common in children; between 2008 and 2010 in the United States, 9.5% of children under the age of 17 had a current asthma diagnosis.¹ In this population, the repercussions of asthma include poor sleep and increased absences from school, in addition to increased medical services.^{1,2} Identification of children at high risk of asthma at an early age is needed for optimal symptom management and possible prevention efforts.^{3,4} Associations between first year of life hospitalization for acute infantile bronchiolitis (AB) and subsequent risk of asthma later in life have frequently been reported,⁵ although whether this association is causal or simply reflects an underlying predisposition towards wheeze is debated.⁶ One non-causal explanation is confounding by risk factors for both AB and asthma. For example, most cases of AB are caused by viral infections, and

viral infections are also common triggers of asthma exacerbations; thus, risk factors that predispose children towards viral infections (e.g., formula vs. breast milk) could be confounders.⁷ Other potential confounders include family history of asthma, gestational age, and environmental factors such as environmental tobacco smoke and air pollution.^{2,5} In a recent review Beigelman and Bacharier speculate that the association between AB and subsequent asthma might be causal for some children (e.g., those hospitalized for AB caused by respiratory syncytial virus infections) and might be a marker of asthma tendency for others (e.g., those with a family history of atopy who have AB caused by human rhinovirus infections).⁷

A recent analysis of data from Swedish population registers found children who were hospitalized for respiratory infections during the first year of life were at 1.5-fold increased risk of asthma after age 5 years, with a 2.2-fold increased risk for children born with a gestational age of less than 28 weeks.⁸ Preterm delivery is a marker of high-risk for both AB and asthma, and the authors postulated that the damage caused by early infections might be exacerbated in extremely preterm infants because these infants have developmental deficits of the airways.⁸ These results suggest biological interaction and may ultimately help clinicians identify children at high risk of asthma, although findings need to be replicated in other settings. In our study we undertook a similar analysis using a linked dataset of emergency department (ED) records and live birth records from the U.S. state of Georgia to investigate whether gestational age modified the association between an ED visit for AB and subsequent risk of an ED visit for asthma after age 5 years.

Methods

A historical cohort of children was assembled using three large administrative datasets. One dataset consisted of all birth records for live born infants in the U.S. state of Georgia between 2002 and 2004 (n=265,590). Staff at the Office of Health Indicators for Planning, Georgia Department of Public Health, routinely link birth records to Georgia death records to identify infant deaths (n=500) and to a database of ED visits assembled by the Georgia Hospital Association. The ED visit database used in this study consisted of all pediatric ED visits in Georgia between January 2002 and June 2010. Birth records were geocoded to Census 2000 block groups using residence at the time of delivery.

The exposure of interest was a dichotomous indicator defined as one or more ED visits before age one year with a recorded ICD-9 code for acute bronchiolitis (AB) (ICD-9 codes 466.1, 466.11, 466.19) in any of the diagnosis fields (n=11,564). The outcome was defined as one or more ED visits after age five years for which asthma was indicated as the primary ICD-9 diagnosis code (ICD-9 codes beginning with 493, n=5,666). Limiting the definition of asthma to visits after age five helps to exclude children who have reactive airway disease at young ages but who do not go on to develop asthma.⁹ In sensitivity analyses we investigate associations using a presumably more sensitive but less specific outcome definition defined as one or more ED visits after age three years for which asthma was indicated as the primary ICD-9 diagnosis code (n=10,505).

The primary analysis compared the risk of asthma among children with AB ($n = 11,564$) with the risk of asthma among children who did not have an ED visit for AB but who utilized the ED for another reason during infancy ($n = 131,694$). We selected this comparison as our primary analysis because of concerns that ED utilization and healthcare-seeking behavior might vary across the socioeconomic gradient. Given the strong association between socioeconomic position and asthma,² comparing children who use the ED during infancy with those who do not might result in confounding. By restricting the “unexposed” to individuals who used the ED during infancy for a reason other than AB we attempted to make the groups exchangeable with respect to healthcare-seeking behavior. We investigated the sensitivity of our results to this decision by also estimating the association of interest using the full cohort of children ($n = 255,473$).

Our dataset lacks information on children who moved out of Georgia during follow-up. To investigate the potential for bias due to loss to follow-up we also performed a case-control analysis where cases were all children who had an ED visit for asthma after age 5 years by June 30, 2010 ($n = 5,666$) and controls were all children who visited the ED at least once after age five years for a reason other than asthma but who had no ED visits for asthma as of June 2010 ($n = 95,475$). This approach ensures that all children being analyzed were still residing in Georgia as of their fifth birthday.

Log-binomial regression was used to estimate crude and adjusted risk ratios, and logistic regression was used to estimate crude and adjusted odds ratios. To control for potential confounding we included natural cubic splines with three degrees of freedom two boundary knots and two internal knots for gestational age (weeks), maternal age (years), birth weight (grams), and percentage of the Census tract living below poverty (Census 2000 estimate). A natural cubic spline on date of birth using two boundary knots and eleven internal knots twelve degrees of freedom over the three-year period was included to account for differences in follow-up time between children. This was done because asthma risks increased with increasing length of follow-up (determined by birth date).

Maternal smoking (yes / no), maternal education (less than high school / high school / more than high school), married (yes / no), maternal race (white / black / other), Medicaid reimbursement of delivery expenses (yes / no), firstborn (yes / no), and infant sex (male / female) were obtained from the birth records and controlled in the model using indicator variables. To investigate effect measure modification of the association between AB and asthma by gestational age we categorized gestational age as extremely preterm (28 weeks or less), early preterm (29–33 weeks), late preterm (34–36 weeks), and full term (37 weeks or more). In these models we replaced the natural spline for gestational age with indicators for the gestational age ranges and included product terms between these indicators and the exposure. Analyses were performed using R 2.15.2.

Results

Of 265,090 births between 2002 and 2004 that survived to age one year, there were 11,564 (4.4%) with one or more ED visits for AB during infancy and 131,694 (49.7%) with at least one ED visit for something other than AB during infancy. Characteristics of these 143,258

children included in the primary analysis are presented in Table 1. Among other differences, children with an ED visit for AB during infancy were more likely to be male, more likely to be born during July-September, and more likely to be born premature. Among the children who used the ED during infancy but who did not have an ED visit for AB, the five most common diagnoses were acute upper respiratory infection, otitis media, fever, pharyngitis, and gastrointestinal illness.

Crude risks of one or more asthma ED visit after age five through June 2010 are shown in Table 2. Risks were higher among children who had an ED visit for AB during infancy across all gestational age categories. Prematurity was also associated with increased risk. Crude and adjusted risk ratios for the association between one or more ED visit for bronchiolitis during infancy and the risk of an ED visit for asthma after age five are shown in Table 23. Visit to the ED for bronchiolitis and risk of asthma was 1.89 [95% confidence interval (CI) 1.73, 2.108] following adjustment for confounders. Inclusion of product terms between gestational age and exposure did not suggest effect modification of the risk ratio between AB and asthma; ($P = 0.78$). Although confidence intervals were wide, there was no evidence to support the hypothesis that the risk ratio among children born extremely preterm of 1.987 [1.107, 3.327] was different from the risk ratios for the other gestational age ranges.

Results from sensitivity analyses are also shown in Table 32. Results were generally consistent across sensitivity analyses, particularly for the adjusted estimates. In the case-control analysis, the five most common diagnoses among the controls were acute upper respiratory infection, fever, otitis media, pharyngitis, and streptococcal sore throat. Neither sensitivity analysis provided evidence to suggest effect measure modification by gestational age. The adjusted risk ratio for the overall association from the sensitivity analyses with the outcome defined as one or more ED visit for asthma after age three years was 1.93 [1.81, 2.106], a result that was slightly higher, but not substantively different, from the result based on ED visits after age five years. Further results from these models are not shown because they did not differ meaningfully from the primary results.

Comment

We observed a positive association between ED utilization for infantile AB and subsequent ED utilization for asthma after age five. We did not observe evidence to support the hypothesis that associations would be larger among extremely preterm infants. The similarity of the estimates from the sensitivity analyses suggest that differences in ED utilization across socio-demographic groups and loss to follow-up from residential migration did not cause large biases.

Several reasons may explain the discrepancies between our results and the Montgomery et al. findings.⁸ One possibility is random error. The adjusted risk ratio estimate from our study for children < 28 weeks gestation was 1.987 [1.107, 3.327]; although the point estimate was virtually identical to our the same as the overall risk ratio of 1.89, the wide confidence interval is compatible with a higher estimate. Similarly, the hazard ratio relating hospitalization for respiratory infection during infancy with asthma after age five among children < 27 weeks gestation from the Montgomery et al. paper was 2.22 [1.659, 3.109],⁸

and the lower bound of this interval was consistent with their estimates for children of other gestational ages. With further research on this topic, the impact of random error will decrease. Other potential explanations relate to the health outcomes investigated. Whereas Montgomery et al. looked at hospitalization for a wide range of respiratory infections during infancy (including influenza, pneumonia, bronchiolitis, and certain upper respiratory infections), we restricted our analysis to acute bronchiolitis in light of the broad literature base that has documented associations between lower respiratory tract infections, particularly respiratory syncytial virus (RSV) bronchiolitis, and subsequent asthma.¹⁰ Compared with Montgomery et al., however, an important limitation of our study is the reliance on ED visits for ascertainment of asthma. It is certain that there are some children in our cohort who had asthma but who did not utilize the ED, and we were unable to identify and classify these children as asthmatic. Arguably, our reliance on ED visit records resulted in an outcome classification that was more skewed towards the severe end of the asthma spectrum than the definition employed by Montgomery et al., which utilized prescription records in addition to hospital records. Another possible explanation is that the populations of Sweden and the U.S. state of Georgia are different, although it is not clear why these differences would result in extreme premature birth being an effect modifier in one location and not the other.

A limitation of our study is the inability to control for several unmeasured potential confounders, including breastfeeding status, atopy diagnosis, family history of asthma, and various environmental exposures including environmental tobacco smoke, cockroaches and other pests, and air pollutants. Whether this confounding would mask true effect measure modification of the association between AB and asthma risk by gestational age is difficult to surmise. For this to happen, the magnitude (or direction) of the confounding would need to vary appreciably across gestational age strata in such way that it caused the (confounded) stratum-specific associations to become more similar to one another.

Our findings are consistent with existing literature on the association between bronchiolitis in early life and subsequent development of asthma, although our results do not help to resolve questions of underlying etiology.⁶ As work continues into defining the biological mechanisms of asthma, however, clinicians can use this information to identify and potentially treat children at increased risk for asthma, as well as in monitoring at-risk infants as they grow.

Acknowledgments

We thank Tim Lash and Penny Howards for helpful suggestions regarding our analytic approach.

This publication was made possible by NIH grants NIEHS K01ES019877 and NIEHS R03ES018963 as well as US EPA grant R834799. This publication's contents are solely the responsibility of the grantee and do not necessarily represent the official views of the US EPA. Further, US EPA does not endorse the purchase of any commercial products or services mentioned in the publication.

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Table 1

Characteristics of cohort members used in primary analysis.

	One or more ED visits for bronchiolitis (n=11,564) (%)	One or more ED visits for reasons other than bronchiolitis (n=131,694) (%)
Characteristics of Child		
Female	41.5	48.0
Race		
<i>White</i>	45.4	45.6
<i>Black</i>	39.0	40.3
<i>Other/Unknown</i>	15.7	14.0
Birth Season		
<i>Jan–Mar</i>	19.7	24.4
<i>Apr–Jun</i>	23.6	24.4
<i>Jul–Sep</i>	29.9	26.1
<i>Oct–Dec</i>	26.8	25.1
Birth weight	3167 (626) ^a	3215 (587) ^a
Gestational age		
<i>20–28 weeks</i>	1.3	0.7
<i>29–33 weeks</i>	3.2	2.6
<i>34–36 weeks</i>	12.0	10.0
<i>37 weeks</i>	83.5	86.8
Characteristics of Mother		
Used Tobacco While Pregnant	11.0	10.7
<i>Missing</i>	0.1	0.2
Education		
<i>Less than High School</i>	34.6	30.6
<i>High School Diploma or GED</i>	32.9	34.0
<i>College Education or Higher</i>	30.5	34.0
<i>Missing</i>	2.0	1.4
Married	48.2	49.0
Percentage of birth residence Census tract below poverty		
<i>0.0 – 6.57</i>	24.7	22.0
<i>6.58 – 10.91</i>	21.3	19.7
<i>10.92 – 15.97</i>	19.1	19.4
<i>15.98 – 23.59</i>	17.0	18.9
<i>23.60 – 75.65</i>	16.7	18.2
<i>Missing</i>	1.2	1.9
Medicaid coverage of delivery	64.5	62.6
Maternal Age in Years	25.1 (5.9) ^a	25.1 (5.9) ^a

^a Mean (standard deviation)

Table 2

Risk(per 100 children) of one or more asthma emergency department visit after age 5 years through June 2010.^a

	One or more ED visits for bronchiolitis (n=11,564)	One or more ED visits for reasons other than bronchiolitis (n=131,694)
Overall	4.5	2.3
Extreme Preterm 20–28 weeks	9.7	5.6
Early Preterm 29–33 weeks	5.6	3.5
Late Preterm 34–36 weeks	5.5	2.8
Term 37 weeks	4.3	2.2

^a Risk through June 2010 is the average risk across children born during 2002–2004 who contributed varying amounts of follow-up time to the analysis.

Table 3

Crude and adjusted risk ratios (RR) and odds ratios (OR) and 95% confidence intervals for associations between first-year of life emergency department visits for acute infantile bronchiolitis and a subsequent emergency department visit for asthma after age 5 years, stratified by gestational age.

	Primary Analysis ^a		Full Cohort ^b		Case-control ^c	
	Crude RR	Adjusted RR ^d	Crude RR	Adjusted RR ^d	Crude OR	Adjusted OR ^d
Overall	2.0 [1.8, 2.1]	1.9 [1.7, 2.1]	2.2 [2.1, 2.5]	2.0 [1.9, 2.2]	2.1 [2.0, 2.4]	2.0 [1.8, 2.2]
Extreme Preterm 20–28 weeks	1.7 [1.0, 3.0]	1.9 [1.1, 3.3]	2.0 [1.2, 3.5]	2.0 [1.2, 3.5]	1.9 [1.0, 3.5]	1.9 [1.0, 3.5]
Early Preterm 29–33 weeks	1.6 [1.0, 2.5]	1.6 [1.0, 2.5]	1.8 [1.2, 2.8]	1.6 [1.1, 2.5]	1.7 [1.1, 2.7]	1.6 [1.0, 2.7]
Late Preterm 34–36 weeks	2.0 [1.6, 2.5]	1.9 [1.5, 2.4]	2.3 [1.8, 2.9]	2.1 [1.7, 2.6]	2.1 [1.6, 2.7]	2.0 [1.5, 2.6]
Term 37 weeks	1.9 [1.8, 2.1]	1.9 [1.7, 2.1]	2.2 [2.0, 2.5]	2.1 [1.9, 2.3]	2.2 [1.9, 2.4]	2.1 [1.9, 2.3]

^aThe primary analysis is a cohort study comparing the risk of asthma among children with an emergency department (ED) visit for acute infantile bronchiolitis (AB) (n = 11,564) with the risk of asthma among children who did not have an ED visit for AB but who utilized the ED for another reason during infancy (n = 131,694).

^bSensitivity analysis using the full cohort of children (n = 255,473) who survived to age 1 year.

^cSensitivity analysis using a case-control design with cases defined as children with one or more ED visit for asthma after age 5 years (n = 5,666) as of June 2010 and controls defined as children who visited the ED at least once after age five years but had no ED visits for asthma after age 5 years as of June, 2010 (n = 95,475). Estimates of association from the case-control design are odds ratios.

^dAdjusted for maternal age, birth weight, and percentage of Census tract below poverty (based on address from birth record) using natural cubic splines (with 2 internal knots); date of birth using a natural cubic spline (with 11 internal knots); and maternal smoking, maternal education, marital status, maternal race, Medicaid reimbursement of delivery expenses, firstborn, and infant sex using indicator variables. The adjusted model for the overall association also includes control for gestational age using a natural cubic spline (with 2 internal knots).