
Paediatric and Perinatal Epidemiology

doi: 10.1111/ppe.12150


Brief report

# Gestational Age-Specific Associations between Infantile Acute Bronchiolitis and Asthma after Age Five

Matthew J. Strickland,[a,b] Caitlin A. Marsh,[b] Lyndsey A. Darrow[b]

[a]*Department of Environmental Health*

[b]*Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA*

## Abstract

***Background:*** Infantile acute bronchiolitis (AB) is a risk factor for the development of paediatric asthma. The associations might differ according to gestational age.

***Methods:*** Data sets of emergency department (ED) visits (January 2002 to June 2010) and livebirth records (January 2002 to December 2004) from the state of Georgia were linked for all children who survived 1 year. Exposure was an ED visit for AB during infancy, and the outcome was an ED visit for asthma after age 5 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 utilised 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:*** Unadjusted 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 1.9 [95% confidence interval 1.7, 2.1]. 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 5; associations did not vary meaningfully by gestational age. Sensitivity analyses did not suggest large biases due to differences in ED utilisation across sociodemographic groups or loss to follow-up from residential migration.

**Keywords:** *bronchiolitis, asthma, emergency department, cohort, preterm, gestational age, premature.*

Asthma is a complex disease common in children; between 2008 and 2010 in the US, 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 hospitalisation for infantile acute 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 hospitalised for AB caused by respiratory syncytial virus (RSV) 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).[8]

A recent analysis of data from Swedish population registers found children who were hospitalised for respiratory infections during the first year of life were

*Correspondence:*
Matthew J. Strickland, Department of Environmental Health, Rollins School of Public Health, Emory University, 1518 Clifton Rd NE, Atlanta, GA 30322, USA.
E-mail: mjstric@emory.edu

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.[9] 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.[9] 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 data set of emergency department (ED) records and livebirth records from the US 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 data sets. One data set consisted of all birth records for liveborn infants in the US 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 paediatric 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 1 year with a recorded International Classification of Diseases, Ninth Revision (ICD-9) code for 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 5 years for which asthma was indicated as the primary ICD-9 diagnosis code (ICD-9 codes beginning with 493, $n = 5666$). Limiting the definition of asthma to visits after age 5 helps to exclude children who have reactive airway disease at young ages but who do not go on to develop asthma.[10] 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 3 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 utilised the ED for another reason during infancy ($n = 131\,694$). We selected this comparison as our primary analysis because of concerns that ED utilisation and health care-seeking behaviour might vary across the socio-economic gradient. Given the strong association between socio-economic 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 health care-seeking behaviour. 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 data set 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 30 June 2010 ($n = 5666$) and controls were all children who visited the ED at least once after age 5 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 analysed were still residing in Georgia as of their fifth birthday.

Log-binomial regression was used to estimate unadjusted and adjusted risk ratios, and logistic regression was used to estimate unadjusted and adjusted odds ratios. To control for potential confounding, we included natural cubic splines with two boundary knots and two internal knots for gestational age (weeks), maternal age (years), birthweight (grams), and percentage of the census tract living below poverty (Census 2000 estimate). A natural cubic spline on date of birth using 2 boundary knots and 11 internal knots over the 3-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), first-born (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 categorised 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 (R Core Team, Vienna, Austria).

## Results

Of 265 090 births between 2002 and 2004 that survived to age 1 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 through September, and more likely to be born preterm. 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.

Unadjusted risks of one or more asthma ED visit after age 5 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. unadjusted 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 5 are shown in Table 3. Visit to the ED for bronchiolitis and risk of asthma was 1.9 [95% confidence interval (CI) 1.7, 2.1] 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 CIs were wide, there was no evidence to support the hypothesis that the risk ratio among children born extremely preterm

**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 | | |
| White | 45.4 | 45.6 |
| Black | 39.0 | 40.3 |
| Other/unknown | 15.7 | 14.0 |
| Birth season | | |
| January to March | 19.7 | 24.4 |
| April to June | 23.6 | 24.4 |
| July to September | 29.9 | 26.1 |
| October to December | 26.8 | 25.1 |
| Birthweight | 3167 (626)[a] | 3215 (587)[a] |
| Gestational age | | |
| 20–28 weeks | 1.3 | 0.7 |
| 29–33 weeks | 3.2 | 2.6 |
| 34–36 weeks | 12.0 | 10.0 |
| ≥37 weeks | 83.5 | 86.8 |
| Characteristics of mother | | |
| Used tobacco while pregnant | 11.0 | 10.7 |
| Missing | 0.1 | 0.2 |
| Education | | |
| Less than high school | 34.6 | 30.6 |
| High school diploma | 32.9 | 34.0 |
| College education or higher | 30.5 | 34.0 |
| Missing | 2.0 | 1.4 |
| Married | 48.2 | 49.0 |
| Percentage of birth residence census tract below poverty | | |
| 0.0–6.57 | 24.7 | 22.0 |
| 6.58–10.91 | 21.3 | 19.7 |
| 10.92–15.97 | 19.1 | 19.4 |
| 15.98–23.59 | 17.0 | 18.9 |
| 23.60–75.65 | 16.7 | 18.2 |
| Missing | 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).
ED, emergency department; GED, General Educational Development.

**Table 2.** Risk (per 100 children) of one or more asthma emergency department (ED) 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 2002–04 who contributed varying amounts of follow-up time to the analysis.

of 1.9 [95% CI 1.1, 3.3] was different from the risk ratios for the other gestational age ranges.

Results from sensitivity analyses are also shown in Table 3. 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 3 years was 1.9 [95% CI 1.8, 2.1], a result nearly identical to the result based on ED visits after age 5 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 utilisation for infantile AB and subsequent ED utilisation for asthma after age 5. 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

**Table 3.** Unadjusted and adjusted risk ratios (RR) and odds ratios (OR) and 95% confidence intervals for associations between first year of life emergency department (ED) visits for acute infantile bronchiolitis and a subsequent ED visit for asthma after age 5 years, stratified by gestational age

| | Primary analysis[a] | | Full cohort[b] | | Case–control[c] | |
|---|---|---|---|---|---|---|
| | Unadjusted RR | Adjusted RR[d] | Unadjusted RR | Adjusted RR[d] | Unadjusted 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] |

[a]The primary analysis is a cohort study comparing the risk of asthma among children with an 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 utilised the ED for another reason during infancy ($n = 131\,694$).

[b]Sensitivity analysis using the full cohort of children ($n = 255\,473$) who survived to age 1 year.

[c]Sensitivity analysis using a case–control design with cases defined as children with one or more ED visit for asthma after age 5 years ($n = 5666$) as of June 2010 and controls defined as children who visited the ED at least once after age 5 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.

[d]Adjusted for maternal age, birthweight, 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, first-born, 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).

suggests that differences in ED utilisation across sociodemographic 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.[9] One possibility is random error. The adjusted risk ratio estimate from our study for children ≤28 weeks gestation was 1.9 [95% CI 1.1, 3.3]; although the point estimate was the same as the overall risk ratio, the wide CI is compatible with a higher estimate. Similarly, the hazard ratio relating hospitalisation for respiratory infection during infancy with asthma after age 5 among children ≤27 weeks gestation from the Montgomery *et al*. paper was 2.2 [95% CI 1.6, 3.1],[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 hospitalisation for a wide range of respiratory infections during infancy (including influenza, pneumonia, bronchiolitis, and certain upper respiratory infections), we restricted our analysis to AB in light of the broad literature base that has documented associations between lower respiratory tract infections, particularly RSV bronchiolitis, and subsequent asthma.[11] 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 utilise 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 utilised prescription records in addition to hospital records. Another possible explanation is that the populations of Sweden and the US state of Georgia are different, although it is not clear why these differences would result in extreme preterm birth being an effect modifier in one location and not in the other.

A limitation of our study is the inability to control for several unmeasured potential confounders, including breast-feeding 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 aetiology.[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.

## Acknowledgements

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.

## References

1 National Center for Health Statistics. *National Surveillance of Asthma: United States 2001–2010, Vital and health statistics, series 3: analytical and epidemiological studies, no. 35.* Hyattsville, MD: National Center for Health Statistics, 2012. DHHS publication no. (PHS) 2013-1419.

2 Follenweider FM, Lambertino A. Epidemiology of asthma in the United States. *Nursing Clinics of North America* 2013; 48:1–10.

3 Sly P, Boner A, Bjorksten B, Bush A, Custovic A, Eigenmann PA, *et al*. Early identification of atopy in the predication of persistent asthma in children. *Lancet* 2008; 372:1100–1106.

4 Azad MB, Coneys JG, Kozyrskyj AL, Field CJ, Ramsey CD, Becker AB, *et al*. Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis. *BMJ (Clinical Research Ed.)* 2013; 347:f6471.

5 Sing 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. *American*

*Journal of Respiratory and Critical Care Medicine* 2007; 175:108–119.
6 Wu P, Hartert TV. Evidence for a causal relationship between respiratory syncytial virus infection and asthma. *Expert Review of Anti-infective Therapy* 2011; 9:731–745.
7 Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. *Current Opinion in Allergy and Clinical Immunology* 2013; 13:211–216.
8 Tsukagoshi H, Ishioka T, Noda M, Kozawa K, Kimura H. Molecular epidemiology of respiratory viruses in virus-induced asthma. *Frontiers in Microbiology* 2013; 4:278.
9 Montgomery S, Bahmanyar S, Brus O, Hussein O, Kosma P, Palme-Kilander C. Respiratory infections in preterm infants and subsequent asthma: a cohort study. *BMJ Open* 2013; 3:e004034.
10 National Heart Lung and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute (US), 2007. NIH publication no. 07-4051.
11 Szabo SM, Levy AR, Gooch KL, Bradt P, Wijaya H, Mitchell I. Elevated risk of asthma after hospitalization for respiratory syncytical virus infection in infancy. *Paediatric Respiratory Reviews* 2013; 13 (Suppl. 2):S9–S15.