

Environmental factors association between asthma and acute bronchiolitis in young children—a perspective cohort study

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Abstract Acute bronchiolitis and asthma are respiratory tract diseases of childhood that are characterized by wheezing. However, the diagnosis of asthma is difficult in patients younger than 2 years. We evaluated the association between asthma or acute bronchiolitis and various risk factors in young children. This perspective cohort study included a study group of children younger than 2 years with a recorded diagnosis of acute bronchiolitis ($N=4,586$) as well as a control group ($N=4,263$). Children in both groups were registered between January 1, 2004 and December 31, 2004, on the Taiwan Longitudinal Health Insurance Database (2005), and each child was followed in our study until December 31, 2006, using data from the same source. Of the 8,849 children in our study, 355 experienced asthma during the 3-year follow-up period. Among these 355 asthma patients, 332 children (29.1 per 1,000 person-years, 95% CI 26.2–36.4) belonged to the acute bronchiolitis cohort and 23 children (2.0 per 1,000 person-years, 95% CI 13.3–29.9) belonged to the comparison cohort. Cox proportional hazard regression analysis showed that children with acute bronchiolitis were more likely to have asthma than the control population, after adjustment for potential confounders (adjusted hazard ratio [HR] 13.55, 95% CI 8.87–20.71). Boys with

acute bronchiolitis had a higher HR for asthma than girls during the 3-year follow-up. Children with acute bronchiolitis who lived in rural areas had a 1.49 HR for asthma compared with their urban counterparts. Children living in the northern region of Taiwan had a higher HR ratio than those in other regions. Sex, urbanization, and geographic region all showed significant associations with acute bronchiolitis and asthma. Based on the asthma-free survival curves of Kaplan–Meier analysis in our study, young children with acute bronchiolitis should be monitored for 2 years to prevent them from developing asthma. This was the first study to evaluate the length of time for which acute bronchiolitis poses a risk for the development of asthma in young children.

Keywords Acute bronchiolitis · Asthma · Risk factors · Bootstrap sensitivity analysis · Epidemiology

Abbreviations

AAP	American Academy of Pediatrics
LHID	Longitudinal Health Insurance Database
NHRI	National Health Research Institute
NHIRD	National Health Insurance Research Database
CysLT	Cysteinyl leukotriene
GINA	Global Initiative for Asthma

Introduction

Acute bronchiolitis is a common cause of lower respiratory tract disease in young children. The condition was first described as “congestive catarrhal fever” more than 150 years ago, with the diagnosis including the clinical manifestation of fever, rhinorrhea, wheezing, crepitations, dyspnea, and difficulty feeding [13]. Although “bronchiolitis” means inflammation of the bronchioles, this characteristic can

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rarely be observed directly but must rather be inferred in young children. The presentation includes respiratory distress in association with signs of viral infection [24]. The American Academy of Pediatrics (AAP) guidelines define bronchiolitis as “a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than 2 years of age” [1, 24]. Most infants recover from acute bronchiolitis in several weeks but may develop recurrent wheezing [15]. Infants with bronchiolitis who develop symptoms severe enough to warrant hospitalization are at increased risk for developing recurrent wheezing and infantile asthma [23].

To date, the pathogenetic basis for the relationship between acute bronchiolitis and asthma has not been clearly elucidated [14]. Clinical diagnosis of asthma is difficult if the patient is younger than 2 years. The length of time for which acute bronchiolitis poses a risk for the development of asthma has also not yet been clearly established. We used a large data set and several independent variables to investigate the relationship between acute bronchiolitis and asthma in young children.

Methods

Study population and study design

The study cohort and comparison group were drawn from the Longitudinal Health Insurance Database (LHID) of Taiwan. The study cohort comprised all patients who received a diagnosis of acute bronchiolitis (ICD-9-CM code 466.1) between January 1, 2004, and December 31, 2004. We excluded patients younger than 2 years to minimize the risk of diagnostic inaccuracy; we also excluded patients who had been diagnosed with asthma before 2004. Furthermore, we included only patients who had received at least three consecutive diagnoses of acute bronchiolitis (ICD-9-CM code 466.1). Our final study cohort included 4,586 patients with acute bronchiolitis.

For the comparison cohort, we excluded patients who had diagnosed with asthma before they developed acute bronchiolitis between 2004 and 2006. We also excluded patients older than 2 years. We assigned their first ambulatory care visits between January 1, 2004 and December 31, 2004, as the entry date. Our final control cohort included 4,263 patients.

Endpoint of the study

In Taiwan, diagnosis of asthma is based on Global Initiative for Asthma (GINA) guidelines. According to the rule of the National Health Insurance Institute in Taiwan, children with

asthma diagnosis should have positive data describing past history, drug history, family history, atopy history, total IgE, allergen-specific test and lung function test or asthma control score. We ascertained an asthma diagnosis by selecting only study cohort patients who had received at least three consecutive diagnoses of asthma (ICD-9-CM code 493) by physicians. All patients in both the study and comparison cohorts were then individually followed from their entry date until they either developed asthma (ICD-9-CM code 493) or until December 31, 2006

Longitudinal Health Insurance Database (2005)

All data were obtained from the LHID2005, which is accessible to researchers who wish to track longitudinal changes related to medical utilization. The National Health Insurance (NHI) program was established in Taiwan in 1995 and it currently has over 25 million enrollees; that is, approximately 99.9 % of the entire Taiwanese population. The Taiwan National Health Research Institute (NHRI) administers the LHID2005, which contains the complete original claims data for 1,000,000 NHI beneficiaries. This subset of the NHI data was obtained by random sampling of the Registry for Beneficiaries (2005) of the National Health Insurance Research Database (NHIRD). The full registry contains data of approximately 25.56 million patients. According to the NHRI reports, no significant differences exist for either age or sex distribution ($\chi^2=0.008$, $df=1$, P value=0.928) between the LHID2005 and NHIRD [20].

To classify a patient's urbanization level, all 359 cities or towns in Taiwan are stratified into seven levels according to standards published by the NHRI. Level 1 refers to “most urbanized” and 7 refers to “least urbanized.” For our study, levels 1 and 2 were combined into a single group, referred to as urban; levels 3 and 4 were combined into a single group, referred to as suburban; and the remaining 3 levels (5, 6, and 7) were combined into a single group, referred to as rural. Geographic location in Taiwan was separated into four regions. The northern region of Taiwan included Taipei City, Keelung City, Taipei County, Taoyuan County, Hsinchu County, and Ilan County. The central region of Taiwan included Taichung City, Miaoli County, Taichung County, Nantou County, Changhua County, and Yunlin County. The southern region of Taiwan included Kaohsiung, Tainan, Chiayi County, Tainan County, Kaohsiung County, Pingtung County, and Penghu County. The eastern region of Taiwan included Taitung County and Hualien County.

Statistical analysis

Pearson's chi-squared test was used to compare group differences for categorical variables (sex, urbanization level, and geographic region). Student's t test was used to compare

group differences for patient's age. We used the Kaplan–Meier method to estimate the cumulative asthma-free survival curve, and the log-rank test to examine the differences in the risk of asthma between the 2 cohorts. Confidence intervals (CI) for the incidence rates were established by calculating the Poisson CI. We also evaluated the asthma-free survival rate using Cox regression models. The regression estimated the hazard ratios (HR) for asthma between the two cohorts after adjusting for the patient's age (treated as a continuous variable) and the categorical variables of sex, urbanization level, and geographic region. To meet the proportional hazards assumption, each dichotomous variable in the model was checked for proportionality by investigative diagnostic log–log survival plots. All data analyses were performed using the SAS statistical package (SAS 9.1.3; SAS Institute Inc. Cary, NC, USA). A *P* value below 0.05 was considered statistically significant.

Sensitivity analysis

We performed bootstrapped sensitivity analysis, which is a robust method for validating Cox regression models [7, 17]. Patients were required to have had at least 1 year of follow-up and could not have had an asthma diagnosis within the first year. We further bootstrapped sensitivity analysis stratified by sex. Girls versus boys were required to have had at least 1 year of follow-up and could not have had an asthma diagnosis within the first year. The bootstrap HR corresponded to the median HR observed among 1,000 replications and the 95% CI to use the bootstrap bias-corrected and accelerated bootstrap [6].

Results

The study cohort included 4,586 children identified as having been diagnosed with acute bronchiolitis, and the comparison cohort included 4,263 children without acute bronchiolitis. The children's demographic characteristics, namely age, sex, urbanization, and geographic region are significantly different between the two cohorts (Table 1). Figure 1 displays the survival curves based on Kaplan–Meier analysis for asthma in children with acute bronchiolitis and in the comparison cohort during the 3-year follow-up.

Table 2 shows the incidence of asthma in children with acute bronchiolitis versus the comparison cohort. Of the 8,849 children included in our study, 355 experienced asthma during the 3-year follow-up, including 332 children (29.1 per 1,000 person-years, 95% CI 26.2–36.4) in the acute bronchiolitis cohort and 23 children (2.0 per 1,000 person-years, 95% CI 13.3–29.9) in the comparison cohort. Boys had a higher rate of asthma than girls (34.3 per 1,000

Table 1 Demographic characteristics for acute bronchiolitis patients and patients in the control patients, 2004 (*N*=8,849)

Variable	Acute bronchiolitis patients <i>n</i> =4,586		Control patients <i>n</i> =4,263		<i>P</i> value
	Total no.	%	Total No.	%	
Characteristics					
Age, Mean (SD)	0.91 (0.52)		0.77 (0.62)		< 0.001
Gender					< 0.001
Male	2,624	57.2	2,013	47.2	
Female	1,962	42.8	2,250	52.8	
Urbanization level					<0.001
Urban	2,444	53.3	2,544	59.7	
Suburban	1,542	33.6	1,284	30.1	
Rural	600	13.1	435	10.2	
Geographic region					<0.001
Northern	2,162	47.1	2,267	53.2	
Central	1,296	28.3	906	21.3	
Southern	1,045	22.8	944	22.1	
Eastern	83	1.8	146	3.4	

person-years, 95% CI 30.2–38.9 for boys; 18.6 per 1,000 person-years, 95% CI 15.3–22.6 for girls).

In the Cox proportional hazard regression analysis (Table 3), the results were adjusted for age, sex, geographic region, and urbanization level. The HR (after adjustment) for asthma during the 3-year follow-up was

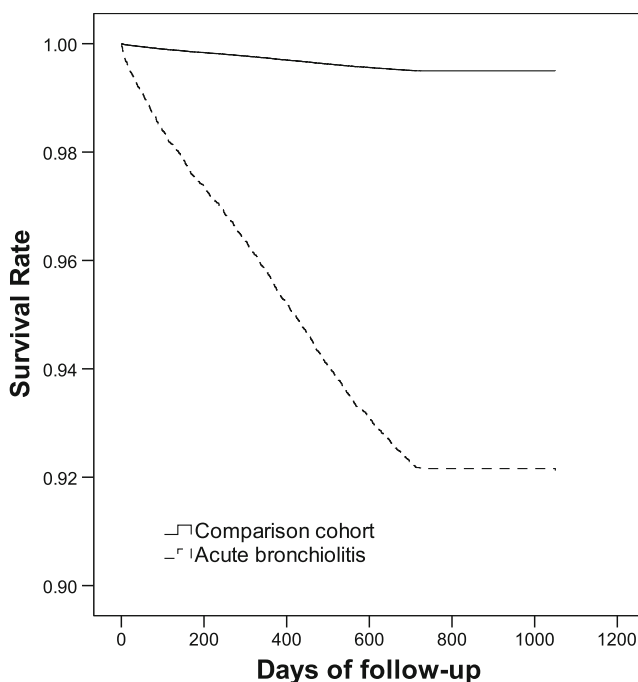


Fig. 1 A plot of asthma-free survival curves based on the Kaplan–Meier analysis for patients with Acute bronchiolitis and comparison cohort

13.55 (95% CI=8.87–20.71) for children with acute bronchiolitis relative to the comparison cohort. Age, sex, urbanization, and geographic region all emerged as variables significantly associated with asthma. These results are discussed later in this paper.

To ensure the validity of our analysis, a series of sensitivity analyses using a bootstrap approach was performed. The adjusted HR for asthma in children with acute bronchiolitis was 5.00 (95% CI, 3.22–8.58) relative to the comparison cohort; this analysis excluded cases in which asthma occurred within the first year of follow-up. We conducted further analyses stratified by sex, again excluding asthma cases occurring within the first year of follow-up (Table 4). The adjusted HR for asthma in boys with acute bronchiolitis was 4.26 (95% CI, 2.58 to 8.58) relative to the comparison cohort. The adjusted HR for asthma in girls with acute bronchiolitis was 6.75 (95% CI, 3.52 to 19.10) relative to the comparison cohort. However, the actual incidence of asthma was higher in boys than girls (Tables 2 and 3). Thus, the adjusted HR (relative to the comparison group) for asthma in children with acute bronchiolitis was slightly higher for girls than for boys.

Discussion

Bronchiolitis has been documented recently, with symptoms including increased airway secretion, mucosal edema, and infiltration of inflammatory cells [2, 11]. Asthma is another chronic respiratory disorder characterized by

Table 2 Incidence and 95% confidence intervals (CIs) for asthma among the acute bronchiolitis patients during up to 3-year follow-up period ($N=8,849$)

Presence of asthma	Total sample	Controls	Patients with acute bronchiolitis
Up to 3-year follow-up period			
Yes	355	23	332
person-years	22,943.7	11,552.5	11,391.2
Incidence per 1,000 person-years	15.5 (13.9–17.2)	2.0 (1.3–3.0)	29.1 (26.2–36.4)
Male			
Yes	254	15	239
person-years	12,408.1	5,444.5	6,963.6
Incidence per 1,000 person-years	20.5 (18.1–23.1)	2.7 (1.7–4.5)	34.3 (30.2–38.9)
Female			
Yes	109	8	101
person-years	11,523.5	6,108.1	5,415.5
Incidence per 1000 person-years	9.4 (7.8–11.4)	1.3 (0.7–2.6)	18.6 (15.3–22.6)

Table 3 Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for Asthma among the Acute bronchiolitis patients during the 3-year follow-up period ($N=8,849$)

Variable	Presence of asthma			
	Crude HR	95% CI	Adjusted HR	95% CI
Acute bronchiolitis	13.94	9.13–21.26	13.55	8.87–20.71
Age (years)	1.44	1.25–1.66	1.48	1.28–1.71
Gender (M)	2.17	1.73–2.72	1.89	1.51–2.37
Urbanization level				
Urban	1(Ref)		1(Ref)	
Suburban	1.35	1.08–1.70	1.56	1.23–1.98
Rural	1.40	1.02–1.92	1.49	1.08–2.06
Geographic region				
Northern	1(Ref)		1(Ref)	
Central	0.65	0.49–0.85	0.44	0.34–0.59
Southern	0.54	0.40–0.73	0.45	0.34–0.61
Eastern	0.69	0.34–1.41	0.71	0.35–1.44

airway inflammation, hyperreactivity, and remodeling of the airways [4]. The etiology of most atopic diseases, including asthma, is complex and can involve genetics, immunologic response, and environmental exposure [4, 18]. The mechanisms underlying the increased incidence of wheezing or asthma after severe bronchiolitis remain unclear [23]. Recurrent wheezing is associated with eosinophilia and eosinophil activation [10], which involves the release of eosinophil granule proteins. Such proteins may include eosinophil cationic protein, cysteinyl leukotrienes, and cytokines capable of

Table 4 Sensitivity analysis—bootstrap hazard ratio point estimates for asthma with acute bronchiolitis patients compare with controls and empirical 95% CIs

Presence of asthma	Bootstrap hazard ratio	
	Acute bronchiolitis patients compare with controls	Empirical 95% CI (BCa)
At least 1 year of follow-up (could not have had a asthma in the first 1 year)	5.00 ^a ($P=0.001$)	3.22–8.58
Stratified by sex (could not have had a asthma in the first 1 year)		
At least 1 year of follow-up; Female children	6.75 ^b ($P=0.001$)	3.52–19.10
At least 1 year of follow-up; Male children	4.26 ^b ($P=0.001$)	2.58–8.58

BCa bootstrap bias-corrected and accelerated

^a Adjustments are made for patient's age, sex, urbanization and geographic region

^b Adjustments are made for patient's age, urbanization, and geographic region

damaging the airways [8]. The level of cysteinyl leukotriene (CysLT) is elevated in asthma patients and is also increased during respiratory syncytial virus bronchiolitis [5, 15]. Respiratory syncytial virus is responsible for a substantial proportion of cases of asthma exacerbation in young children [9]. Severe respiratory syncytial virus bronchiolitis early in life is associated with a high incidence of asthma and eczema [4]. However, Koponen et al. [16] reported that non-respiratory syncytial virus bronchiolitis and maternal asthma were independently significant early-life risk factors for asthma. Cytokines also play a role in acute bronchiolitis and asthma. The percentage of bronchoalveolar lavage eosinophil has been found to correlate significantly with levels of BAL IL-5 in both asthma and bronchiolitis patients [14]. Lower IFN- γ production at the time of bronchiolitis is an indicator of poorer pulmonary function and increased responsiveness to histamine, 4.9 months after bronchiolitis, and is also related to the development of asthma after bronchiolitis in infants [21].

We investigated several variables to establish whether they were risk factors influencing the development of acute bronchiolitis into asthma. We analyzed patient age and sex as well as environmental data, namely urbanization and geographic region. We found that acute bronchiolitis occurred frequently in Taiwanese children aged approximately 1 year. The ratio for acute bronchiolitis was 1.33 for boys relative to girls. The HR for asthma was 1.89 for boys relative to girls. During the 3-year follow-up, boys with acute bronchiolitis showed a higher incidence of asthma than girls with acute bronchiolitis. However, at the 1-year follow-up mark, the HR analysis for acute bronchiolitis patients compared with control patients showed that girls were slightly more at risk for asthma than boys. Sigures et al. [22] reported that the male sex is a risk factor for all types of wheezing disorders at age 7. Our results suggested that sex plays an important role at different ages.

Our analysis of urbanization level showed that acute bronchiolitis occurred more frequently in children living in urban areas than in children living rurally. Urban areas are usually crowded, and one might expect a higher incidence of bronchial diseases as a result. However, our analysis showed that among children with acute bronchiolitis, rural location was associated with a 1.49 HR relative to urban location. We concluded that children living in rural areas may have lower access to treatment facilities for acute bronchiolitis, compared with children in urban areas. Thus, children living rurally might develop asthma because of chronic inflammation of the airways.

Our analysis of the geographic region showed that acute bronchitis occurred more frequently in children living in the northern region of Taiwan than in any other region. Children living in the northern region also had a higher HR for asthma compared with other regions. In northern Taiwan,

the climate is usually colder and moister than other regions. Odds of developing acute bronchiolitis because of the bad weather are relatively high, with a related possibility of continuing to develop asthma. A separate study showed that bronchiolitis occurring in different seasons is associated with different degrees of risk for developing asthma [3]. Carroll et al. [3] reported that children with asthma had a history of infant bronchiolitis, with 24 % of cases occurring during the winter virus season. We similarly found that children with acute bronchiolitis had a 13.55 HR for asthma compared with the control cohort, after adjustment for age, sex, geographic region, and urbanization level. Based on the asthma-free survival curve generated in our analysis, we suggest that children with acute bronchiolitis should be regularly followed up and observed closely for at least 2 years. The children's parents should be educated and advised regarding possible symptoms, to help prevent the development of asthma during the 2 years.

Recent studies on bronchiolitis or asthma have focused on genetic factors. A genetic link between viral bronchiolitis and asthma has been proposed, and candidate gene associations related to bronchiolitis have been reported [12]. However, only one study to date has examined the occurrence of asthma after bronchiolitis [12]; this was a family-based association study of 134 children with bronchiolitis in the United Kingdom. A variant in the promoter region of the IL-8 gene was transmitted significantly more often than expected in children who had persistent wheezing [12]. Thus, genetic factors and immune response may play a role in the pathway from bronchiolitis to asthma [23]. However, Mansbach et al. [19] reported that vitamin D status was a potential cofactor for severe bronchiolitis to develop into asthma. A number of factors, including genetics and nutrition, are likely to influence the progression of acute bronchiolitis into asthma.

Conclusion

In young children, the occurrence of acute bronchiolitis is strongly correlated with the later development of asthma. Environmental factors may increase the risk association between acute bronchiolitis and asthma. In Taiwan, residing in a rural area or the northern region of the country is associated with increased risk for early childhood asthma. All children diagnosed with acute bronchiolitis should be monitored for at least 2 years thereafter, to minimize their risk of developing asthma.

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