

ORIGINAL ARTICLE

Urbanization factors associated with childhood asthma and prematurity: a population-based analysis aged from 0 to 5 years in Taiwan by using Cox regression within a hospital cluster modelSheng-Chieh Lin, MD^{1,2} and Hui-Wen Lin, PhD^{3,4}¹Department of Pediatrics, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan, ²Department of Pediatrics, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ³Department of Mathematics, Soochow University, Taipei, Taiwan, and ⁴Evidence Based Medicine Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan**Abstract**

Objective: Childhood asthma and premature birth are both common; however, no studies have reported urbanization association between asthma and prematurity and the duration of prematurity affect asthma development. We use Taiwan Longitudinal Health Insurance Database (LHID) to explore association between asthma and prematurity among children by using a population-based analysis. **Methods:** This is a retrospective cohort study with registration data derived from Taiwan LHID. We evaluated prematurely born infants and children aged <5 years ($n=532$) and age-matched control patients ($n=60505$) using Cox proportional hazard regression analysis within a hospital cluster model. Of the 61 037 examinees, 14 012 experienced asthma during the 5-year follow-up, including 161 (72.26 per 1000 person-years) infants and children born prematurely and 13 851 (40.27 per 1000 person-years) controls. **Results:** The hazard ratio for asthma during 5-year follow-up period was 1.95 (95% confidence interval = 1.67–2.28) among children born prematurely. Boys born prematurely aged 0–2 years were associated with higher asthma rates compared with girls in non-premature and premature groups. Living in urban areas, those born prematurely were associated with higher rates of asthma compared with non-prematurity. Those born prematurely lived in northern region had higher asthma hazard ratio than other regions. **Conclusion:** Our analyses indicated that sex, age, urbanization level, and geographic region are significantly associated with prematurity and asthma. Based on cumulative asthma-free survival curve generated using the Kaplan–Meier method, infants born prematurely should be closely monitored to see if they would develop asthma until the age of 6 years.

Keywords

Asthma, epidemiology, pediatrics, prematurity, prevention, risk factors, robust sandwich variance

History

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Introduction

Asthma is a common disease of the respiratory tract that manifests as inflammatory process during childhood. Although understanding of asthma has increased considerably, its precise cause remains unknown, and the complex relations among the genetic, immunologic, pharmacologic, and environmental factors associated with the disease require further investigation [1]. Studies have indicated that the immune system response is the major factor influencing the development of childhood asthma since postnatal period [2]. *In utero* and perinatal factors might also increase the risk of developing asthma [2,3]. Infants exposed to urinary tract infections and the premature rupture of membranes *in utero* was associated with increased risk of hospital admission for

childhood asthma [2]. Perinatal factors play a role in developing childhood asthma; however, the etiology might differ in early- (0–2 years of age) and late- (at the age of 3 years or later) onset asthma [4]. Goyal et al. [5] suggested that birth at late-preterm and low-normal gestational ages might represent a risk factor for developing asthma and the increased use of health services during early childhood. Crump et al. [6] observed increased risk of asthma among patients of extreme preterm gestational age, which lasted at least into young adulthood. A review study also demonstrated that preterm babies are associated with increased risk of asthma compared with term babies [7]. However, in Abe et al. [8], late preterm birth was not associated with a diagnosis of asthma in early childhood. Demissie et al. [9] also reported that prematurity is not associated with asthma after active management during pregnancy. Therefore, the pathogenic basis between prematurity and asthma remains ambiguous [7,8].

According to our research, Musafiri et al. [10] reported that adult asthma in urban area was higher prevalence than rural

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area. But, no clinical study has described the urbanization factors associated with asthma development in preterm babies and duration of prematurity affect asthma development. We hypothesize that urbanization is an independent risk factor for prematurity with childhood asthma. In this study, we used a population-based analysis to evaluate the relation between prematurity and asthma. We choice children less than 5 years of age and evaluate the relation between prematurity and early- (0–2 years of age) and late- (3–5 years of age) onset asthma.

Patients and methods

Study population and design

In Taiwan, National Health Insurance Program for single payer was launched on 1 March 1995. National Health Insurance Program is compulsory social insurance. Almost people in Taiwan joined this program. For example, 22.60 million of Taiwan's 22.96 million populations were enrolled in this program at the year of 2007. Foreigners in Taiwan are also eligible for this program. The act of this program is to provide health service including illness, injury or maternity. Longitudinal Health Insurance Database (LHID) is a registration data of everyone who was a beneficiary of the National Health Insurance Program. This database contains registration files and original claim data for reimbursement. Bureau of National Health Insurance (BNHI) of Taiwan collects these data including ICD-9-CM code from the National Health Insurance Program and sorts it into data files providing scientists in Taiwan for research purposes.

Data regarding this study population were derived from the Longitudinal Health Insurance Database 2005 (LHID2005) in Taiwan, which contains all the original claims data from one million patients who were randomly sampled from the 25.56 million insurants in the 2005 registry of the National Health Insurance Research Database (NHIRD); thus, the LHID2005 is a large and reliable database and numerous studies using LHID2005 data have been published in peer-reviewed journals [11]. The retrospective cohort study was selected from the LHID2005, comprising all patients born prematurely (ICD-9-CM code 765). Patients aged >5 years were excluded. The cohort included 532 premature patients, who were also divided into 2 subgroups: preterm infants <1500 g ($n=70$) and preterm infants >1500 g ($n=462$). The comparison cohort was retrieved from the remaining patients in the LHID 2005 and also excluded patients aged >5 years. The comparison cohort comprised 60505 infants and children. To classify the patient urbanization level, all 359 cities or towns in Taiwan were stratified into 7 levels based on the NHRI standards, ranging from Level 1, “most capitalized” to Level 7, “least capitalized.” In this study, Levels 1 and 2 were combined into a single group, referred to as urban; Levels 3 and 4 were combined as suburban; and the Levels 5, 6, and 7 were combined as rural. Geographic location in Taiwan was separated into 4 regions including Northern, Central, Southern and Eastern Taiwan.

Outcome variable

Asthma (outcome variable) was identified by selecting study and comparison cohort patients who were diagnosed with

asthma (ICD-9-CM code 493) during the follow-up. In Taiwan, a diagnosis of asthma is based on the Global Initiative for Asthma guidelines (GINA) [12]. According to the rules of the National Health Insurance Institute in Taiwan, children diagnosed with asthma should have positive data describing their medication and family histories, history of atopy, total immunoglobulin E (IgE) count, allergen-specific and lung function test results, and asthma control scores. All patients in the study and comparison cohorts were individually followed up for a diagnosis of asthma from 1 January 2004 to 31 December 2008 for 5 years.

Statistical analysis

In this study, the effects of various hospitals on outcome were considered. A robust sandwich covariance matrix estimate was used to consider hospital clusters and ensure robust results. The Cox regression models described by Lee et al. [13] were used to conduct a robust sandwich covariance matrix estimate to account for intracluster dependence between hospital clusters. The asthma-free survival rates were evaluated using a Cox regression model within a hospital cluster, and the hazard ratios (HRs) for asthma were compared between the cohorts after adjusting for patient age (continuous), sex, urbanization level and geographic region. The detailed robust sandwich covariance matrix estimate is displayed in the Appendix. Pearson's chi-square tests were used to compare the group differences regarding categorical factors and Student's t tests were used to compare group differences regarding continuous factors (Table 1). The Kaplan–Meier method was used to estimate the cumulative asthma-free survival curve, and the log-rank test was used to examine the differences in the risk of asthma between the cohorts (Figure 1). All data analyses were conducted using the SAS statistical package (SAS9.1.3; SAS Institute Inc, Cary, NC) and a p value of <0.05 was considered significant.

Table 1. Demographic characteristics for prematurity children and control cohort, 2004–2008 ($N=61037$).

	Prematurity patients <i>n</i> = 532		Control <i>n</i> = 60505		
Variable	Total no. (%)		Total no. (%)		<i>p</i> Value
Characteristics	Year		Year		
Age, Mean (SE)	0.89 (0.05)		2.78 (0.01)		<0.001
Age, Median(IQR)	1 (0–1)		3 (1–4)		<0.001
Mean for follower up (SE)	4.19 (0.06)		5.68 (0.01)		<0.001
Mean for asthma survival time (year, SE)	7.2 (0.18)		8.3 (0.12)		<0.001
Gender					0.192
Male	294	55.3	31 719	52.4	
Female	238	44.7	28 786	47.6	
Urbanization level					0.291
Urban	469	88.2	53 092	87.7	
Suburban	58	10.9	6299	10.4	
Rural	5	0.9	1114	1.8	
Geographic region					0.799
Northern	266	50.0	29 244	48.3	
Central	123	23.1	15 092	24.9	
Southern	131	24.6	14 818	24.5	
Eastern	12	2.3	1351	2.2	

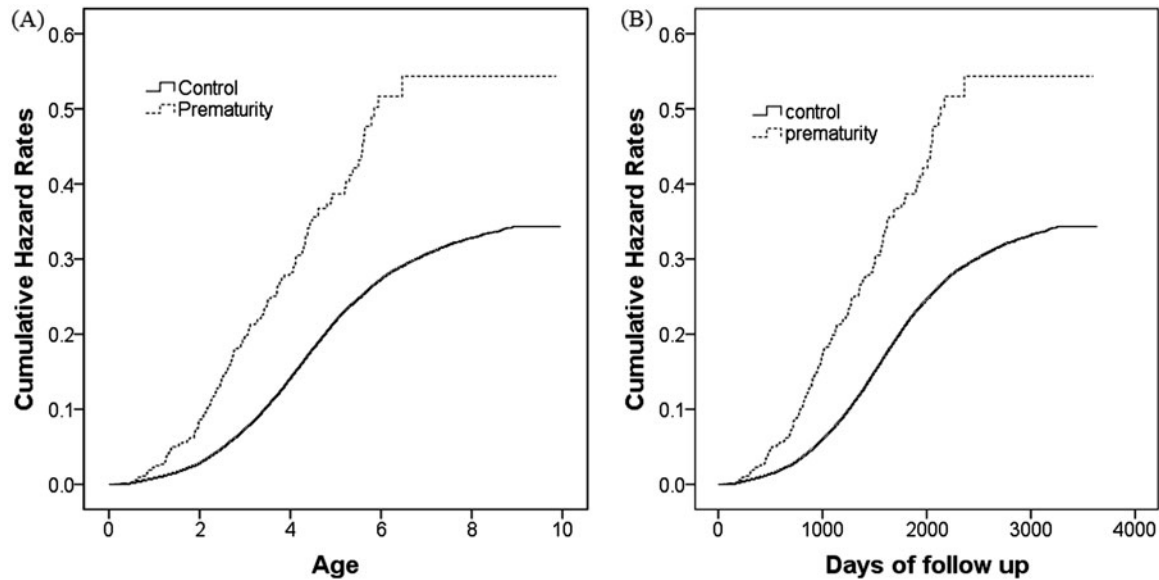


Figure 1. A plot of asthma hazard rate curves based on the Kaplan-Meier analysis for patients with prematurity children and control cohort by years of (A) age and (B) days.

Results

In this study, we evaluated 532 prematurely born infants and children and 60 505 controls. The baseline variables (sex, urbanization level and geographic region) displayed no significant differences between the cohorts (Table 1). Figure 1(A) displays the HR curves based on the Kaplan–Meier method, indicating a higher risk of asthma among the prematurely born infants and children than in the comparison cohort by the years of age ($p<0.001$). Figure 1(B) displays the HR curves based on the Kaplan–Meier method, indicating a higher risk of asthma among the prematurely born infants and children than in the comparison cohort during the days of follow-up ($p<0.001$).

Table 2 displays the data regarding the presence of asthma among the premature and comparison cohorts. Of the 61037 infants and children evaluated, 14012 experienced asthma during the 5-year follow-up, including 161 (72.26 per 1000 person-years) born prematurely and 13 851 (40.27 per 1000 person-years) controls. As shown in Table 1, the cohorts displayed significant differences in age ($p<0.001$). To reduce deviation caused by age, we subdivided the patients into 2 age groups. We then identified the rates of asthma development as 74.38 per 1000 person-years among those born prematurely aged 0–2 years, and 59.56 per 1000 person-years among those born prematurely aged 3–5 years, during the 5-year follow-up. In a Cox proportional hazard regression analysis, using a hospital cluster model, the HR of asthma during the 5-year follow-up was 1.95 (95% CI = 1.67–2.28) among all patients born prematurely, 1.53 (95% CI = 1.31–1.78) among those aged 0–2 years, and 1.56 (95% CI = 1.07–2.27) among those aged 3–5 years, in comparison with non-prematurity within the same age cohort. The adjusted HR for asthma was 1.73 (1.13–2.61) among preterm infants weighing <1500 g, and 1.42 (1.23–1.62) among preterm infants weighing 1500–2500 g, in comparison with non-prematurity groups. The HRs for asthma were higher among the preterm infants weighing 1500–2500 g and <1500 g compared with

Table 2. Incidence and 95% confidence intervals (CIs) for asthma among the prematurity and non-prematurity children during 5-year follow-up period ($N = 61\,037$).

	Total sample	Controls	Prematurity patients
Presence of asthma			
Follow-up period			
Yes	14012	13 851	161
Person-years	346 171	343 942	2228
Incidence per 1000 person-years	40.47	40.27	72.26
Crude HR ^a	–	1.00	1.95 (1.67–2.28)
Age 0–2			
Yes	5591	5449	142
Person-years	112 037	110 128	1909
Incidence per 1000 person-years	49.90	49.47	74.38
Adjusted HR ^b	–	1.00	1.53 (1.31–1.78)
Age 3–5			
Yes	8421	8402	19
person-years	234 134	233 814	319
Incidence per 1000 person-years	35.97	35.93	59.56
Adjusted HR ^b	–	1.00	1.56 (1.07–2.27)
Adjusted HR (1500 ~ 2500 gams) ^a	–	1.00	1.42 (1.23–1.62)
Adjusted HR (<1500 gams) ^a	–	1.00	1.73 (1.13–2.61)

This model uses a clustered method for the robust sandwich covariance matrix estimation to account for the hospital clustering.
^aAdjustments are made for patient’s age, sex, urbanization and geographic region.
^bAdjustments are made for patient’s sex, urbanization and geographic region.

the control group. Table 3 displays the adjusted HRs for asthma according to a multivariable Cox proportional hazard regression analysis within a hospital cluster model. The adjusted HR for asthma during the 5-year follow-up was 1.45 (95% CI = 1.27–1.67) among the prematurely born infants and children. Variables such as age, sex, urbanization

level, and geographic region were significantly associated with asthma development. Figure 2 displays the asthma rates among boys and girls of various ages, geographic regions, and urbanization levels in the control and premature groups.

Table 3. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for asthma among the prematurity and non-prematurity children during the 5-year follow-up period ($N = 61\,037$).

Variable	Presence of asthma		
	Adjusted HR	95% CI	<i>p</i> Value
Prematurity patients	1.45	1.27–1.67	<0.001
Age (years)	0.85	0.84–0.86	<0.001
Gender (M)	1.34	1.30–1.39	<0.001
Urbanization level			
Rural	1(Ref)		
Suburban	1.25	1.08–1.45	<0.001
Urban	1.07	0.93–1.23	0.326
Geographic region			
Northern	1(Ref)		
Central	0.69	0.64–0.74	<0.001
Southern	0.56	0.52–0.60	<0.001
Eastern	0.73	0.62–0.85	0.002

This model uses a clustered method for the robust sandwich covariance matrix estimation to account for the hospital clustering.

Discussion

Asthma is an obstructive respiratory disorder characterized by airway inflammation, hyper-reactivity, and remodeling of the airways, clinically manifesting as wheezing [1]. Prematurity is defined as birth at a gestational age <37 weeks. Rona et al. [14] reported that gestational age is associated with the respiratory symptom of wheezing, and that each additional week of gestation reduces the risk of wheezing in childhood by approximately 10%. In Lu et al. [15], children born extremely prematurely were associated with high incidence of persistent lung function abnormalities. According to spirometry findings, these children displayed obstructive airway patterns during lung development and those born extremely prematurely remained at high risk of airway obstruction, deficits in lung function, and increased bronchial responsiveness during long-term follow-up (11 years) [15]. According to Jaakkola et al. [7], the active treatment of physiological airflow obstructions in prematurity might protect preterm babies against asthma development. A large proportion of children born prematurely with impaired lung function might not receive the appropriate treatment [16]. Therefore, the early evaluation of premature babies is crucial for monitoring asthma development.

In this study, we investigated several variables to establish whether they were risk factors influencing the development of asthma among children born prematurely. We analyzed

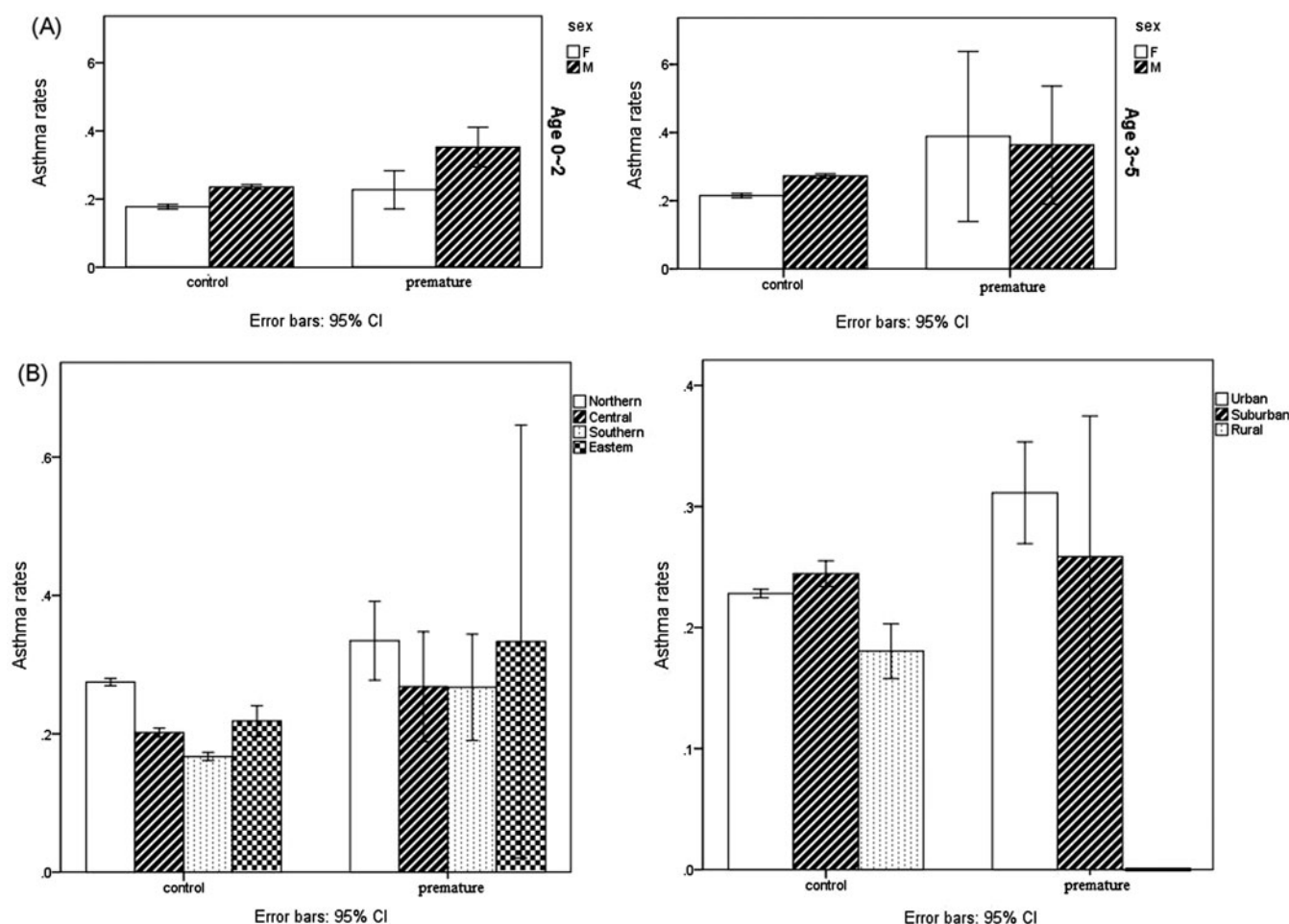


Figure 2. (A) Asthma rates at various ages among boys and girls in the control and premature groups. (B) Asthma rates in various geographic regions and urbanization levels among the control and premature groups.

patient age and sex, as well as environmental data such as urbanization level and geographic region. We identified that prematurity is more common among boys compared with girls in Taiwan at a ratio of 1.237. Boys born prematurely had a 1.34 HR for asthma compared with girls. During the 5-year follow-up, from 0 to 2 years of age, the HR for developing asthma was 1.53 among the premature group compared with the control group. From 3 to 5 years of age, the HR for asthma development was 1.56 in the premature group compared with the control group. As shown in Figure 2(A), from 0 to 2 years, boys were associated with higher rates of asthma than girls were in both the control and premature groups. Premature boys were also associated with higher asthma rates than the male controls. Among children aged 3–5 years, boys were associated with higher asthma rates than the female controls, but not the premature girls. Boys were associated with higher asthma rates than girls were at various ages, whereas premature boys were associated with higher asthma rates than were girls only ages 0–2 years. From 3 to 5 years of age, the rate of asthma development showed nonsignificant differences between premature girls and boys. Baraldi and Filippone [17] reported that infants born prematurely are commonly associated with abnormal lung function during the first 2 years after birth. The current findings indicate that sex plays a major role in asthma development at various ages. Namazy et al. [18] reported girls with early preterm delivery were not associated with increased risk of moderate to severe asthma. According to our findings, we suggest that boys born prematurely should be carefully monitored from birth until 2 years to see if they would develop asthma.

Our analyses of urbanization levels indicated that prematurity are more common among infants and children living in urban areas (prevalence 0.009) compared with those living in rural areas (prevalence 0.004). Among those born prematurely, urban location was associated with a 1.07 HR and suburban location was associated with a 1.25 HR for asthma compared with rural locations. Those born prematurely and living in urban areas were associated with higher asthma rates than non-prematurity as shown in Figure 2(B). We considered that infants and children born prematurely and living in urban areas might have greater access to life-saving facilities compared with those in rural areas; however, these prematurely children might develop asthma because of long-term oxygen treatment, which influences lung development and inflammation. Our analyses of geographic region indicated that prematurity was more common among those living in Northern Taiwan compared with those living in other regions. In Northern Taiwan, the climate is typically colder and more humid compared with other regions. Premature infants and children living in Northern Taiwan exhibited a higher HR for asthma compared with those in other regions. Respiratory syncytial virus (RSV) infection is readily transmitted in cold areas. The infants and children in Southern Taiwan were associated with lower asthma rates than were those living in other regions, and the control cohort was associated with lower asthma rates than the premature group was. The premature infants and children exhibited a 1.45 HR for asthma compared with the controls, after adjusting for age, sex, geographic region, and urbanization

level. Based on our generated asthma HR curve, we suggest that premature infants and children should be regularly followed up and closely observed until the age of 6. The parents should be educated and advised regarding possible symptoms of asthma to facilitate the monitoring of asthma development.

The pathogenic basis between prematurity and asthma is not well established [19]. Prematurity is known to be associated with wheezing caused by infection with the rhinovirus or RSV [20]. The rhinovirus is associated with IgE production and airway inflammation [21]. The RSV is responsible for substantial wheezing and asthma exacerbation among infants and children [22]. For a few weeks after the provision of live attenuated vaccinations, premature infants are associated with reduced risk of wheezing-related lower respiratory diseases [20]. Premature infants are also associated with high risk of rhinovirus and RSV infection and subsequent development of asthma. Certain premature infants develop bronchopulmonary dysplasia (BPD), exhibiting an increased risk of developing severe lung function abnormalities. Children born prematurely without BPD typically exhibit poorer lung function at school age compared with control children [23,24]. Airflow limitations can persist into school age, although most patients display improvements as their age increases [17]. In addition to premature lung development, infection, and BPD, the exposure of the lungs to oxygen among neonatal patients plays a role in the association between prematurity and asthma development. Premature infants placed on ventilators or in a hyperoxic environment inhibit hypoxia-inducible factor 1- α (HIF-1 α) signaling in response to environmental signals [19,25,26]. Epithelial-derived HIF-1 signaling plays a central role in determining the responses of the lungs to allergens. HIF-1 α -mediated transcriptional regulation is critical to the normal development of immunity in the lung [19]. In an animal study, the neonatal loss of HIF-1 α was associated with enhanced response to an allergen, and the induction of Th2-mediated immunity and inflammation [19]. Neonatal epithelial hypoxia inducible factor-1 expression regulates the response of the undeveloped lung, in which immune-mediated inflammation might lead to asthma development [19]. This mechanism might explain the increased incidence of asthma among patients born prematurely. In our study, we still have some limitation. As many factors such as genetic (IL-4 gene), immunologic (RSV, dust mite), pharmacologic (aspirin), and environmental factors (smoking) may affect asthma, we cannot adjust all of these covariate in the regression models. However, we may minimize these influences.

Conclusion

Our results indicate that infants and children with a history of prematurity are strongly associated with asthma development. Those born prematurely and living in urban areas and northern region are associated with an increased risk of childhood asthma. Premature boys aged 0–2 years are also associated with a high risk of developing asthma. All infants born prematurely should be monitored until the age of 6 to see if they would develop asthma.

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Declaration of interest

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Appendix

Robust sandwich variance estimate

For the i th subject, $I = 1, \dots, n$, let T_i be the observed time, w_i be the weight and $Z_i(t)$ be the covariate vector at a time t , with premature children as the variable. Let D_i be the asthma event indicator and let $Y_i(t) = I(T_i \geq t)$. According to Lin and Wei [27], let

$$S^{(r)}(\beta, t) = \sum_{j=1}^n w_j Y_j(t) e^{\beta' Z_j(t)} Z_j^{\otimes r}(t), r = 0, 1$$

and $\bar{Z}(\beta, t) = \frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)}$. The score residual for the i th subject is as follows:

$$L_i(\beta; T) = D_i \{Z_i(T_i) - \bar{Z}(\beta, T_i)\} - \sum_{j=1}^n D_j \frac{w_j Y_j(T_j) e^{\beta' Z_j(T_j)}}{S^{(0)}(\beta, T_j)} \{Z_j(T_j) - \bar{Z}(\beta, T_j)\}.$$

The robust sandwich variance estimate of β by Binder [28] is as follows:

$$\hat{V}(\hat{\beta}) = I^{-1}(\hat{\beta}) \left[\sum_{j=1}^n w_j L_j(\hat{\beta}; T) \right]^{\otimes 2} I^{-1}(\hat{\beta}),$$

where $I^{-1}(\beta)$ is the observed information matrix and $k^{\otimes 2}$ is cross product of k .