

ORIGINAL ARTICLE

Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study

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Abstract

Background: The association between neonatal jaundice and childhood asthma is a new finding of two reports. The purpose of the study was to verify their results.

Methods: Data from 11,321 children were collected from the National Health Insurance Research Database. Their claims data were evaluated from birth to 10 yr old. Children were analyzed as case (those with neonatal jaundice) and controls (those without neonatal jaundice). The diagnostic criteria for asthma were as follows: at least four asthma diagnoses at outpatient services and emergency department (ED), or one asthma diagnosis during an admission. In children fitting the asthma criteria, those with no asthma diagnosis after 1 yr of age were excluded. Mantel–Haenszel's odds ratios were calculated after adjustment for the following confounders: preterm/low birth weight, neonatal infection, other respiratory conditions, other birth conditions, and gender. Asthma rate, onset time, the use of drugs, upper respiratory infection and lower respiratory infection (LRI) rates, hospital admission/ED visit rates, and the effect of phototherapy were evaluated.

Results: After adjustment for the confounding factors, the rate of asthma was higher in icteric children (OR: 1.64, 95% CI 1.36–1.98, $p < 0.001$), and the influence in females was stronger. There still was an association between neonatal jaundice and late onset asthma (asthma onset after 3 yr of age). In asthmatic children, those with neonatal jaundice have increased asthma onset rate before age 6, increased use of inhalant steroids, LRI rates, and ED visits for respiratory disease.

Conclusions: Neonatal jaundice increased the rate and severity of childhood asthma in subjects aged up to 10 yr and may be a risk factor for childhood asthma.

With advances in medicine, pharmacological control of childhood asthma is increasingly effective. However, there is no cure for asthma, and the disease process continues irrespective of therapy. Understanding the way in which the disease evolves in the perinatal period is therefore important, to be able to prevent, rather than control the disease after it has developed (1).

Perinatal risk factors for childhood asthma (AS) such as maternal age and premature have been identified (2). However, there may be other undiscovered risk factors. In our

clinical experience, some children with asthma also have a history of neonatal jaundice. Some studies have indicated that bilirubin has harmful effects, such as inducing inflammation (3) and inducing atopy (4), and that it has adverse effects on lung tissue (5). Therefore, neonatal jaundice may be a risk factor for childhood asthma.

The association was not studied before except the reports by Aspberg et al. They first reported the association between neonatal jaundice and the use of anti-asthma drugs in 1 yr (6), and asthma admission (7). Although pioneered and

potentially useful in the clinical practice, there were some limitations. The use of anti-asthma drugs does not equate to an asthma attack and is far from a diagnosis of asthma. Asthma admission is not equal to the whole profile of asthma.

The National Health Insurance Research Database (NHIRD) is a good representative database, including basic patient data and all medical records, and accurately reflects an objective profile of morbidity in Taiwan (8). By analyzing this large set of representative data, we aimed to investigate the association of the whole profile of neonatal jaundice with childhood asthma and corroborate the findings of Asperg et al. (6, 7)

Methods

Data information

The NHIRD served as our data source (8). The database contains healthcare data on more than 95% of all hospitals and clinics in Taiwan and more than 95% of the population receiving health care (9). The sampled data were taken from a random selection of beneficiaries of the Bureau of National Health Insurance (BNHI) via the Registry for Beneficiaries. The BNHI is the sole buyer of health services. There were no significant differences in the distributions of age, gender, medical care expenses, and geography between the samples and the entire population of 23 million insured subjects. The database provides patient identification numbers, birthdays, gender, diagnostic codes in the ICD-9-CM format, prescription drugs, medical care facilities, and other items.

Data collection, diagnostic codes, and determination of the confounding factors

A total of 11,546 children born between 1997 and 2000 (about 1% of total population in Taiwan born between 1997 and 2000) were randomly selected from the NHIRD. After excluding subjects with questionable basic data, a total of 11,328 children were included. Their claims data from birth to 10 yr of age were analyzed. The ICD-9-CM codes used in our study were presented in Table 1. The definition of neonatal jaundice comes from the record of the NHIRD; over 95% of the diagnosis was made by the pediatrician.

Neonatal infections, neonatal respiratory conditions, preterm/low birth weight, male gender, low socioeconomic status, and urban environment were considered risk factors for asthma. Other birth conditions (see Table 1), such as birth asphyxia (2) and other complications of pregnancy, may affect the development of asthma in children and were also considered a risk factor for asthma. We evaluate whether these factors influenced the asthma development rate. If an influence was noted, the risk factors would be the confounding factors in our study and being adjusted later. The association between early wheezing (accepting bronchodilator more than three times before age one) and neonatal jaundice was evaluated.

Table 1 The ICD-9-CM codes used in our study

Diagnosis	ICD-9
Asthma	493
Neonatal jaundice	774
Infections specific to the perinatal period	771
Other fetal and newborn respiratory conditions	770
Preterm, low birth weight (including slow fetal growth and fetal malnutrition)	764, 765
Other birth conditions	
Fetus or newborn affected by maternal complications of pregnancy	761
Fetus or newborn affected by complications of placenta cord and membrane	762
Fetus or newborn affected by other complications of labor and delivery	763
Birth trauma	767
Intrauterine hypoxia and birth asphyxia	768
Hospital admission/emergency department visits, the diagnosis of respiratory disease	460-519
Upper respiratory infection	460-463, 464.0, 465
Lower respiratory infection	466, 480-486, 464.1-464.5

Doctor-confirmed asthma cases and asthma profiles up to 10 yr of age

The criteria of 'doctor-confirmed asthma' were the following: at least four diagnoses of asthma at outpatient services and emergency department (ED), or one diagnosis of asthma during an admission during the age of 1–10 yr old. Because early wheezing might be misdiagnosed as asthma, in children fitting the asthma criteria mentioned earlier, those with no asthma diagnosis after 1 yr of age were excluded. Those with neonatal jaundice (exposed) were classified as the study group or icteric children. Those without (non-exposed) were classified as the control group or non-icteric children. After adjusting for the confounding factors, we compared how many children in both groups had asthma in the subsequent 10 yr of life (the asthma rate). After excluding children with asthma onset before 3 yr of age and adjusting for the confounding factors, we compared late onset asthma rate (where first asthma presentation was after the third birthday) in different groups.

We assumed that the confounding factors (preterm/low birth weight, neonatal infection, other respiratory conditions, and other birth conditions) would influence the drug use and complications and that the incidence of these factors would be unequally higher in the icteric children. To prevent the interference, we excluded those with confounding factors. In asthmatic and non-asthmatic children, we compared the incidence rates of first asthma diagnosis (asthma onset time), use of bronchodilators/inhaled steroids (steroids or corticosteroid/long-acting beta2 agonist combinations), number of upper respiratory infection (URI) and lower respiratory tract infection (LRI), hospital admission/ED visits with respiratory disease in both groups. The drugs were chosen according to the anatomic therapeutic chemical (ATC) codes: adrenergics,

inhalation (R03A), adrenergics, systemic (R03C), xanthines (R03DA), inhaled steroids (R03BA), and corticosteroid/long-acting beta2 agonist combinations (R03AK06 and R03AK07). The association between phototherapy and asthma was evaluated too.

Statistical analysis

All analyses were performed using SAS version 9.1 for windows (SAS Inc., Cary, NC, USA) and SPSS 12.0 (SPSS Inc, Chicago, IL, USA). Statistical analysis was performed using Mantel-Haenszel analysis after adjustment for the confounders. Odds ratios (OR) were determined as risk estimates, and their 95% confidence intervals (CI) were estimated. The t-test was used for differences in the prevalence of the use of drugs, number of asthma attacks, number of URI/LRI, and hospital/ED visits between groups. Two-sided p values of <0.05 were considered to be significant. Figures were created using SigmaPlot (Systat Software, San Jose, CA, USA).

Results

Demographics and determination of confounding factors

Eleven thousand three hundred and twenty-one children were recruited (male 49% and female 51%). The neonatal jaundice rate was 6.3% (717 cases), and 61.4% of these 717 cases underwent phototherapy. The overall asthma rate was 17.0% (males 21.4% and females 12.7%). The rate in different groups and genders was presented in Table 2.

Socioeconomic status and urban/country environment were not statistically significantly associated with asthma or jaundice. Others five factors, preterm/low birth weight, neonatal infections, other respiratory conditions, other birth conditions, and gender, were significantly associated with asthma and jaundice. Therefore, the five factors were the confounding factors in our study and were subsequently adjusted for in the analysis. After adjusting for relevant confounders, the

association between neonatal jaundice and early wheezing was not statistically significant ($p = 0.067$).

Asthma rates, asthma onset time, and the use of drugs in different groups

After adjusting for the five confounding factors, there was a statistically significant association between neonatal jaundice and asthma overall, in males and in females. The influence was stronger in female than in male. Late asthma onset rate was still higher in icteric children (Table 2). After adjusting for the five confounding factors plus early wheezing, there was still a statistically significant association between neonatal jaundice and asthma (OR: 1.53, 95% CI 1.27–1.85, $p < 0.001$). The asthma onset time, after excluding those with confounding factors, is presented in Fig. 1. The rates in the icteric children were higher before age 6. There were no differences in the use of bronchodilators in both groups. The use of inhaled steroids in the asthmatic children, after excluding those with confounders, is presented in Fig. 2. After age 5, the use of inhaled steroids was higher in the icteric children. The use of bronchodilators in asthmatic children was higher than that in non-asthmatic children in both groups. But in asthmatic children, the use of bronchodilators was the same in both groups.

Other clinical parameters and the influence of phototherapy

The clinical parameters, after excluding those with confounding factors, are presented in Table 3. In asthmatic children, the average numbers of LRI and ED visit in icteric children were significantly higher than that in non-icteric children. In non-asthmatic children, the average numbers of URI, LRI, and ED visit and admission in icteric children were significantly higher. There were no differences in the average numbers of asthma attacks in asthmatic case in different groups.

Of the icteric children who underwent phototherapy, 28.2% developed asthma, and 27.4% of the icteric children

Table 2 Demographic data and asthma rate

Variable		Study group (icteric children)	Control group (Non-icteric children)	Odds ratio (95% CI)	p-value
Subjects	Total	717 (6.3%)*	10604 (93.7%)*		
	Male	436 (7.8%)*	5121 (92.2%)*		
	Female	281 (4.9%)*	5483 (95.1%)*		
Asthma	Total	200 (27.9%)†	1724 (16.3%)†	1.64 (1.36–1.98)	<0.001
	Male	137 (31.4%)†	1052 (20.5%)†	1.59 (1.26–2.00)	<0.001
	Female	63 (22.4%)†	672 (12.3%)†	1.74 (1.27–2.39)	<0.001
Late onset asthma‡	Total	80 (13.4%)§	849 (8.7%)§	1.41 (1.07–1.84)	0.013

Control group: percent of late onset asthmatic case in total non-icteric children.

*Study group: percent of subjects with jaundice in total children, total male, and total female. Control group: percent of subjects without jaundice in total children, total male, and total female.

†Study group: percent of asthmatic case in total icteric children, icteric male, and icteric female. Control group: percent of asthmatic case in total non-icteric children, non-icteric male, and non-icteric female.

‡After excluding children with asthma onset before 3 yr of age, we compared late onset asthma rate (where first asthma presentation was after the third birthday) in different groups.

§Study group: percent of late onset asthmatic case in total icteric children.

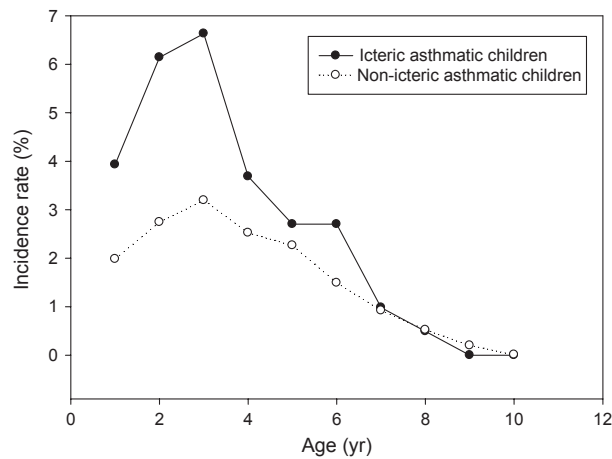


Figure 1 Incidence rates of a first diagnosis of asthma (asthma onset time) at different ages. Those with confounding factors were excluded.

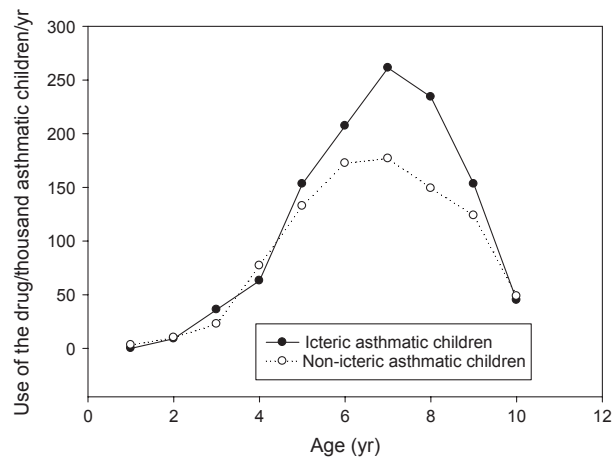


Figure 2 The use of inhaled steroids (steroids or corticosteroid/long-acting beta2 agonist combinations) in asthma children. Those with confounding factors were excluded.

who did not undergo phototherapy developed asthma. There was no statistically significant association between phototherapy and the development of asthma after adjustment for confounding factors (OR: 1.03, 95% CI 0.72–1.47, $p = 0.958$).

Discussion

We found an association between neonatal jaundice and asthma. Asperg et al. (6, 7) first found the association (anti-asthma drug use at 1 yr, but no definite diagnosis), and our study verified their finding. Asthma diagnoses made by doctors and an observation period in our study also supplement their limitation. Although the rate of asthma was lower in females (12.7%) than in male (21.4%), the odds ratio of an increased asthma rate in the icteric children was higher in females (OR: 1.74) than in males (OR: 1.59). This indicates

that the influence of jaundice in the development of asthma in females is stronger than in males. We did not find an association between phototherapy and asthma in contrast to previous studies (6). In Taiwan, phototherapy is arranged for those with serum bilirubin levels of higher than 15 mg/dl, and differences in the criteria for treatment may explain this difference.

Bronchiolitis and early onset transient wheeze at early age might be misdiagnosed as asthma. In our asthma definition, those with no asthma diagnosis after 1 yr of age were excluded. An association between neonatal jaundice and late onset asthma was also noted (Table 2). Therefore, the misdiagnoses rate could be decreased in our study. A higher rate of LRI and ED visit was noted in the icteric asthmatic children. Higher rate of URI, LRI, ED visit, and admission was noted in the icteric non-asthmatic children (Table 3). This might suggest that neonatal jaundice influences not only the lower airway (asthma) but also the upper airway (URI) or be associated with allergic rhinitis, airway hypersensitivity, or immune function and then increase healthcare utilization. This also suggested that neonatal jaundice not only increases the asthma rate but also increases the severity of the disease. However, future study is necessary to verify our hypothesis.

In comparison with non-icteric asthmatic children, icteric asthmatic children have early onset disease with increased later use of inhaled corticosteroids (Figs 1 and 2) and no influence on bronchodilator use. This indicates that the influence of jaundice on airway is not restricted to early age, but also lasted to late age, and the mechanism is inducing airway chronic inflammation, remodeling, or lung growth, rather than acute broncho-constriction.

The immunologic mechanisms underlying the jaundice effect on asthma formation remain unknown. From lecture review, we find studies supporting the effect. Although bilirubin is considered as an antioxidant (10), the role of antioxidants in infants has not been definitively clarified, and bilirubin level does not exert a meaningful antioxidant effect in preterm infants (11). Studies indicated that bilirubin above 12.5 mg/dl is a strong prooxidant (3). In icteric children, the increased catabolism of fetal hemoglobin results in an increase of heme, a potentially prooxidant and harmful molecule (12). Hence, bilirubin/heme might induce airway inflammation and of asthma.

To prevent maternal immune rejection, fetal immune circumstance was toward a Th-2 phenotype during pregnancy (13). After birth, there must be a rapid down-regulation of the Th-2 phenotype and up-regulation of Th-1 to prevent the development of allergic sensitization (1). The study of Liu et al. (14) indicated that bilirubin could inhibit Th-1 cell response. In icteric infants, the inhibition of a Th-1 cell response indicates that they are still under the Th-2 phenotype after birth, leading to an increase in the development of allergic diseases.

It is well-known that differences in intestinal bacterial flora in infants influence the development of allergic diseases (15). In icteric children, the amount of bile secreted into the intestine is different from those without jaundice, and this may result in different types of intestinal flora (16). Other studies

Table 3 The average numbers of the asthma visits, URI, LRI, hospital admission, ED visit per year per case in the 10 yr of age in different groups. Those with confounding factors were excluded

	Asthmatic children			Non-asthmatic children		
	Icteric	Non-icteric	p	Icteric	Non-icteric	p
	Frequency*	Frequency*		Frequency*	Frequency*	
Numbers of asthma visit	1.53	1.51	0.887	NA†	NA†	NA†
Numbers of URI	11.4	10.8	0.272	9.06	7.43	<0.001
Numbers of LRI	4.31	3.78	0.050	2.52	1.85	<0.001
Numbers of admission‡	0.15	0.13	0.262	0.06	0.03	<0.001
Numbers of ED visit‡	0.44	0.31	0.006	0.21	0.13	<0.001

ED, emergency department; LRI, lower respiratory infection; URI, upper respiratory infection.

*Frequency: average numbers per year per case.

†Asthma visit records in non-asthmatic children were doubtful and not applicable.

‡Hospital admission and ED visit because of respiratory disease.

have also indicated that intestinal microflora affect serum bilirubin levels (17). Therefore, the difference of intestinal flora between icteric and non-icteric infant might influence the development of allergic disease.

One study indicated that intracellular accumulation of unconjugated bilirubin inhibits the production of interleukin-2 (4). As IL-2 is a Th-1 cytokine, a reduction in IL-2 will skew the Th-1/Th-2-balance toward Th-2, which is typical in atopic individuals. The other study indicated that bilirubin exerts a detrimental effect on lung surfactant surface tension properties (5). Finally, unconjugated bilirubin has been shown to decrease the activity of antibody-dependent cellular cytotoxicity (ADCC) (18), and a reduced ADCC capacity *in vitro* correlates with a susceptibility to asthma (19).

There were no data on cesarean delivery, maternal age, maternal smoking during pregnancy, and low Apgar scores in our study. One study indicated that maternal smoking during pregnancy was associated with asthma in those under 2 yr of age, and maternal age was associated with asthma in those aged 2 and over (20). In our study, the influence of asthma was not restricted to an age younger or older than 2 yr, and therefore, the influence of these two factors may be excluded. The findings of Aspberg et al. (6), after adjusting for cesarean delivery, maternal age, maternal smoking during pregnancy, and low Apgar score, also noted an association between neonatal jaundice and asthma. Their finding might supplement our limitation.

There was no information available from NHIRD on breastfeeding/formula feeding for these children, and some late-preterm birth might not be included in our premature subjects. The association between late-preterm birth and early

wheezing was noted (21). Although the association between early wheezing and neonatal jaundice was not significant ($p = 0.067$), we cannot actually exclude the possibility that late-preterm births were confounding the association between neonatal jaundice and asthma. To resolve the problem, we adjust for the five confounding factors plus early wheezing, and a statistically significant association between neonatal jaundice and asthma was still noted. Therefore, we could decrease the interference of early wheezing and indirectly decrease the interference of late-preterm birth. Breastfeeding increased the rate of neonatal jaundice and might confound our study results. Breastfeeding clearly protects against early wheezing, but its effect on late asthma was controversial (22). Excluding those with no asthma diagnosis after 1 yr of age and adjusting early wheezing may decreased the interference of feeding mode in our study. The association between neonatal jaundice and late onset asthma could also decrease the confounded effect of feeding mode. However, future study is necessary to evaluate the influences of the factors mentioned earlier.

From our results and a review of the literature, an association between neonatal jaundice and asthma in children was strongly suggested, and the influence in females is stronger. We also found that neonatal jaundice increased the rate of chronic airway inflammation and/or remodeling, numbers of URI, LRI, and ED visits and admission. A prospective cohort study with careful documentation of all potential confounders including mode of delivery, gestation, and mode of feeding is necessary to confirm the association. Mechanistic studies are also needed to understand better how neonatal jaundice might influence asthma risk.

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