

Neonatal urinary tract infection may increase the risk of childhood asthma

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Abstract The aim of this population-based retrospective cohort study was to investigate the onset of urinary tract infection in newborns and the associated risks of childhood asthma. Children with neonatal UTI ($n=3,312$) and randomly selected controls ($n=13,243$) were enrolled for our analysis. We calculated the follow-up person-years for each participant from the index date until the diagnosis of asthma, the end of 2008, or withdrawal from the insurance system (because of death or loss to follow-up). Furthermore, we compared the risk of asthma between non-UTI and UTI cohorts by using Cox proportional hazards model analysis, the adjusted hazard ratio (aHR), and a 95 % confidence interval (95 % CI). The overall asthma incidence rate was found to be 1.53-fold significantly higher in the UTI cohort than in the non-UTI cohort (70.3 vs 45.8 per 1000 person-years). After

we adjusted for potential risk factors, the overall risk of asthma remained higher in the UTI cohort (aHR=1.47, 95 % CI=1.35–1.59). The incidence rate was higher in boys than in girls. Overall, patients suffering from UTI may have a greater risk of developing asthma than patients without UTI. This nationwide retrospective cohort study demonstrates that neonatal UTI may increase the risk of childhood asthma.

Introduction

Asthma is the most common chronic respiratory inflammatory disease in childhood, and an increase in the prevalence of asthma in the latter half of the 20th century has been reported [1, 2]. Numerous studies have investigated possible explanations for this increase, but the causes of asthma remain unclear. Increasingly more studies have focused on early-life events, such as respiratory viral infections, that may increase the risk of childhood asthma [3–5]. Other perinatal risk factors—including babies born preterm, of low birth weight, with respiratory distress syndrome or neonatal jaundice, and needing positive pressure ventilation at birth—increased susceptibility to asthma [2, 6, 7]. Numerous studies have suggested that early exposure to infections in utero or early in life is a potentially critical risk factor in the development of allergic disease [6, 8–10]. However, little is known about whether neonatal nonrespiratory bacterial infections, such as neonatal urinary tract infection (UTI), are associated with the risk of childhood asthma.

The National Health Insurance Research Database (NHIRD) is a representative database that includes basic patient data and all medical records and accurately reflects an objective profile of morbidity in Taiwan [11]. We hypothesized that newborns with UTI have an increased risk of childhood asthma compared

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with those without UTI. To test this hypothesis, we conducted a population-based retrospective cohort study by analyzing the NHIRD.

Methods and materials

Data source

The National Health Insurance (NHI) program, launched in 1995, is the largest health insurance program in Taiwan, and the coverage rate has been nearly 99 % of the resident population of Taiwan since 2000. Following Taiwan's implementation of its NHI program, the NHIRD was established by the National Health Research Institutes (NHRI) in 1996. Before the National Health Insurance Research Database (NHIRD) was released for research purposes, the identification of each insurant was encrypted to protect personal privacy.

This study was based on claims data information from a random sample of all insured children under 18 years of age in Taiwan for the 1996–2008 period, which is a subset of the NHIRD. This dataset contains registration files and original claims data for reimbursement, such as information concerning demographic characteristics and diagnosis of disease for each beneficiary.

Study population

We used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to diagnose the disease of each beneficiary in a retrospective cohort study. Several Taiwan studies had demonstrated the high accuracy and validity of ICD-9 diagnosis in NHIRD. Taiwan launched a national health insurance (NHI) in 1995, operated by a single-buyer, the government [7, 12–14]. Medical reimbursement specialists and peer review should scrutinize all insurance claims. The diagnoses of urinary tract infection and asthma were based on the ICD-9 codes which were judged and determined by related specialists and physicians according to the standard criteria. Therefore, the diagnoses and codes for urinary tract infection and asthma used in this cohort study should be correct and reliable.

For enhancing the diagnostic certainty, UTI was defined as the patient having at least one hospital admission or at least two visits for outpatient medical services related to UTI. We established a UTI cohort as patients with newly diagnosed UTI (ICD-9-CM: 599.0 or 771.82) and aged under 1 month for the period 2000–2006 ($n=3,501$). The clinical diagnosis date of the UTI was defined as the index date. We four-fold-frequency-matched the non-UTI participants according to sex, urbanization of residential area, parental occupation, and index dates, to select a comparison cohort ($n=13,992$).

According to the level of population density (people/km [2]), proportion of higher education, size of elderly and agricultural populations, and number of physicians per 100,000 people, we classified urbanization into seven ordered levels (level 1 to 7). Because of the relatively small number of level 6 and level 7 classifications, we combined them with level 5. Level 1 demonstrated the highest levels of urbanization, whereas level 4 was the least urbanized. All of the participants with a history of asthma before the index date, older than 1 month, with vesicoureteral reflux (VUR; ICD-9-CM: 5,937) diagnosis or missing baseline data on birthday or sex were excluded.

Regarding potential risk factors for adjustment, we considered not only demographic characteristic factors (sex, urbanization of residential area, and parental occupation) but also the comorbidity history in both cohorts. A comorbidity date before the index date was defined according to infections (ICD-9-CM: 771), neonatal jaundice (ICD-9-CM: 774), pre-term low birth weight (ICD-9-CM: 764 and 765), and other fetal and newborn respiratory conditions (ICD-9-CM: 770).

Objectives

In this study, our major focus was measuring the occurrence of asthma (ICD-9-CM 493). We calculated the follow-up time in person-years for each participant from the index date until the diagnosis of asthma, the end of 2008, or withdrawal from the insurance system (because of death or loss to follow-up).

Data availability statement

All data and related metadata were deposited in an appropriate public repository. The data on the study population that were obtained from the NHIRD (http://w3.nhri.org.tw/nhird/date_01.html) are maintained in the NHIRD (<http://nhird.nhri.org.tw/>). The NHRI is a nonprofit foundation established by the government.

Ethics statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Patient consent is not required to access the NHIRD. This study was approved by the Institutional Review Board (IRB) of China Medical University (CMU-REC-101-012). The IRB specifically waived the consent requirement.

Statistical analysis

Baseline characteristics of the demographic distributions of sex, urbanization of residential areas, parental occupation, and comorbidity history in the UTI and non-UTI cohorts were

described to analyze the differences in these variables between UTI and non-UTI cohorts by employing a chi-squared test. When the assumption of a chi-squared test was relaxed, we used Fisher's exact test to assess the differences for variables, such as comorbidity of VUR, in the two cohorts. The incidence rate was calculated in both cohorts and stratified according to demographic variables and comorbidity history, to measure the incidence rate ratio (IRR) of asthma in these variables by using Poisson regression analysis. The adjusted hazard ratio (aHR) of asthma and 95 % confidence interval (95 % CI) were estimated using the multivariable Cox proportional hazards model to measure the association between UTI and asthma. Kaplan-Meier cumulative incidence plots in the UTI and non-UTI cohorts were generated showing the amount of time before asthma for all end points, and a log-rank test was employed to assess the differences between the two cumulative incidence curves. Analyses were performed using the SAS 9.3 statistical package (SAS Institute Inc., NC, USA), with $P < 0.05$ in two-tailed tests considered significant.

Results

During the study period, 3312 children with UTI and 13,243 children without UTI were characterized (Table 1). All of the children were younger than 1 month. The UTI and non-UTI

cohorts exhibited similar distributions of demographic variables, but a history of comorbidity was more common in the UTI cohort ($P < 0.0001$). There were no participants with VUR in both cohorts.

Table 2 shows the incidence rate, IRR, and aHR of asthma measured in the UTI and non-UTI cohorts. The overall asthma incidence rate was 1.53-fold significantly higher in the UTI cohort than in the non-UTI cohort (70.3 vs 45.8 per 1000 person-years). After we adjusted for potential risk factors, the overall risk of asthma remained higher in the UTI cohort (aHR=1.47, 95 % CI=1.35–1.59). The incidence rate was higher in boys than in girls. For boys, the aHR of asthma was 1.48 (95 % CI=1.34–1.64) higher for UTI patients than for non-UTI patients. Compared with the non-UTI cohort, the UTI patients' aHR of asthma was 1.44 (95 % CI=1.21–1.72) for level 1 urbanization, 1.49 (95 % CI=1.28–1.72) for level 2 urbanization, 1.40 (95 % CI=1.17–1.69) for level 3 urbanization, and 1.55 (95 % CI=1.33–1.81) for level 4 urbanization. An occupation-specific analysis revealed an incidence of asthma in both cohorts, regardless of parental occupation; however, patients with UTI had a greater risk of asthma than those without UTI. Furthermore, the incidence of asthma for patients with comorbidity was higher than that in patients without comorbidity. The aHR of asthma in the UTI cohort with comorbidity was 1.32 (95 % CI=1.16–1.51) higher than that of the non-UTI cohort with comorbidity.

Table 1 Baseline characteristics of demographics and comorbidity between those with urinary tract infection (UTI) and without urinary tract infection (non-UTI) cohorts

Characteristic	Urinary tract infection				<i>p</i> -value
	No (<i>N</i> =13243)		Yes (<i>N</i> =3312)		
	Number	%	Number	%	
Sex					0.99
Girl	5738	43.3	1435	43.3	
Boy	7505	56.7	1877	56.7	
Urbanization					0.99
1 (highest)	2916	22.0	729	22.0	
2	4088	30.9	1022	30.9	
3	2609	19.7	653	19.7	
4 (lowest)	3630	27.4	908	27.4	
Occupation					0.99
White collar	7612	57.5	1903	57.5	
Blue collar	3401	25.7	851	25.7	
Others	2230	16.8	558	16.8	
Comorbidity					
Infections	299	2.26	1245	37.6	<0.0001
Neonatal jaundice	776	5.86	1206	36.4	<0.0001
Preterm low birth weight	408	3.08	177	5.34	<0.0001
Other fetal and newborn respiratory conditions	302	2.28	136	4.11	<0.0001

Chi-square test for significance; Urbanization: level 1 is the most urbanized and level 5 is the least urbanized

Table 2 Incidence and adjusted hazard ratio of asthma stratified by sex, urbanization, occupation and comorbidity compared between non-UTI and UTI cohorts

Variables	Urinary tract infection						Compared to non-UTI	
	No			Yes				
	Event	PY	Rate	Event	PY	Rate	IRR (95 % CI)	Adjusted HR (95 % CI)
Overall	3220	70,255	45.8	1118	15900	70.3	1.53 (1.43–1.65)***	1.47 (1.35–1.59)***
Sex								
Girl	1185	31,335	37.8	419	7195	58.2	1.54 (1.37–1.73)***	1.44 (1.26–1.66)***
Boy	2035	38,920	52.3	699	8706	80.3	1.54 (1.40–1.69)***	1.48 (1.34–1.64)***
Urbanization								
1 (highest)	685	15,525	44.1	229	3557	64.4	1.46 (1.25–1.70)***	1.44 (1.21–1.72)***
2	1018	21,664	47.0	364	4810	75.7	1.61 (1.42–1.83)***	1.49 (1.28–1.72)***
3	635	13,983	45.4	212	3260	65.0	1.43 (1.21–1.69)***	1.40 (1.17–1.69)***
4 (lowest)	882	19,083	46.2	313	4273	73.2	1.58 (1.37–1.83)***	1.55 (1.33–1.81)***
Occupation								
White collar	1966	40,419	48.6	662	9199	72.0	1.48 (1.35–1.63)***	1.39 (1.25–1.54)***
Blue collar	818	17,663	46.3	291	3955	73.6	1.59 (1.37–1.84)***	1.57 (1.34–1.85)***
Others	436	12,173	35.8	165	2747	60.1	1.68 (1.39–2.02)***	1.61 (1.30–2.00)***
Comorbidity								
No	2864	63,811	44.9	447	6503	68.7	1.53 (1.38–1.70)***	1.51 (1.37–1.67)***
Yes	356	6,444	55.2	671	9398	71.4	1.29 (1.11–1.50)***	1.32 (1.16–1.51)***

PY person-years, Rate incidence rate per 1000 person-years, IRR incidence rate ratio, 95 % CI 95 % confidence interval, Adjusted HR adjusted hazard ratio

Multiple analysis including age, sex, urbanization, occupation and history of comorbidity

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure 1 illustrates that the cumulative incidence of asthma was 9.3 % higher in the UTI cohort than in the non-UTI cohort during a 9-year follow-up period (38.1 % vs 28.8 %; log-rank

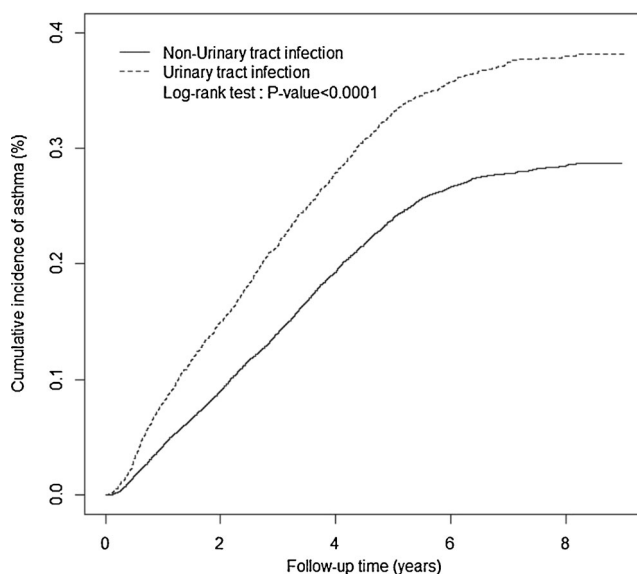


Fig. 1 Cumulative incidence of asthma among patients with urinary tract infection (UTI) (dashed line) and non-urinary tract infection (non-UTI) (solid line)

test < 0.0001). Table 3 shows that the IRR of asthma in the UTI cohort and the non-UTI cohort declined over time. Before the 5-year follow-up, the aHR of asthma was significantly higher in the UTI cohort than in the non-UTI cohort (aHR=2.00 for < 1 -year follow-up, aHR=1.45 for 1–3 years follow-up, aHR=1.33 for 3–5 years follow-up).

Discussion

Based on our research, this is the first population-based retrospective cohort study to demonstrate an association between neonatal UTI and the risk of childhood asthma. This association was independent of other risk factors including age, sex, urbanization, occupation, and comorbidity (adjusted for HR).

The hygiene hypothesis suggests that decreased microbial exposure in childhood leads to an increasing prevalence of UTI and childhood asthma; in other words, a multitude of infectious agents can induce protection from various immunological disorders [15]. Burgess et al. demonstrated that childhood infectious disease protected against asthma persisting in later life but that pertussis and measles were associated with new-onset asthma after childhood [16]. In

Table 3 Incidence and adjusted hazard ratio of asthma by follow-up year in UTI and non-UTI cohorts

Follow time	Urinary tract infection						Compared to non-UTI	
	Event	No PY	Rate	Event	Yes PY	Rate	IRR (95 % CI)	Adjusted HR (95 % CI)
<1	516	13003	39.7	263	3184	82.6	2.08(1.91–2.27)***	2.00(1.67–2.39)***
1–3	1222	23785	51.4	437	5502	79.4	1.55(1.41–1.69)***	1.45(1.28–1.66)***
3–5	1089	18558	58.7	328	4089	80.2	1.37(1.23–1.51)***	1.33(1.15–1.55)***
≥5	393	14909	26.4	90	3125	28.8	1.09(0.94–1.27)	1.08(0.82–1.42)

PY person-years, rate incidence rate per 1000 person-years, IRR incidence rate ratio, 95 % CI 95 % confidence interval, Adjusted HR adjusted hazard ratio

Multiple analysis including age, sex, urbanization, occupation and history of comorbidity

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

addition, Illi et al. reported that endotoxin in a child's mattress was inversely associated with atopic sensitization and asthma [10]. Both of these studies have found that childhood infection agents, but not neonatal infection, had a protective effect against allergic disease.

In a large population-based study, Algert et al. showed that, as in utero exposure to both UTI and preterm, prelabor rupture of membranes carries an increased risk of childhood asthma, immune system response rather than a specific organism [17] may generally be the relevant factor. The findings of McKeever et al. are also inconsistent with the "hygiene hypothesis" [8]. Their study demonstrated sufficient statistical power to examine the effects of 14 types of infection, but without UTI in 6-month intervals from birth. However, none of these personal infections appeared to protect against the development of allergic disease consistently, even after adjustment for consulting behaviour. They also found no consistent evidence that antibiotics increased the risk of developing allergic disease, although there might be an increased risk of early diagnosis of allergic disease with the use of antibiotics.

Montgomery et al. reported that newborns who spent their first night in a communal nursery were at increased risk of developing hay fever because infants in the nursery were more likely subjected to low doses and short durations of nonfamilial microorganisms [18]. The authors speculated that the development of the immune system is strongly influenced by early exposure to infectious agents, potentially leading to dysfunction.

Previous studies have reported that impaired innate immune factors may predispose to infection, particularly rhinovirus, *Streptococcus pneumoniae*, *Salmonella enteritidis*, and *Escherichia coli* [19, 20]. The mechanism in effect indicates that allergic sensitization can induce similar impairment of innate immunity through toll-like receptor signal transduction. Conversely, the infection destroyed the innate immune system, triggered impaired type 1 helper T cells, and induced a sensitization reaction of asthma. This may explain why neonatal urinary infection may present a risk factor for childhood asthma,

because these microorganisms may destroy the naïve innate immune system and play a role in sensitization to asthma.

The merit of this study is that we show an association between UTI and subsequent risk of childhood asthma by using a large population database with minimal selection bias. However, there are some limitations to our study. First, the diagnosis of asthma was based on ICD codes; hence, detailed laboratory data and clinical information, such as C-reactive protein, urine culture, the IgE level, specific IgE, and severity of asthma, was lacking. Second, the data about other potential risks or protective factors beyond the neonatal age are unavailable in the NIRHD. Third, the participants in this study were ethnically Chinese; thus, the results might not be applicable to other populations. Fourth, follow-ups do not extend beyond a participant's eighth birthday. Finally, the use of antibiotics in early infancy has been observed to substantially increase the risk of asthma between the ages of 5 and 10 [21]. There is still no evidence showing that the use of antibiotics in newborns causes a risk of childhood asthma; therefore, confounding risks associated with antibiotics or UTI will require careful control study.

In conclusion, neonatal UTI may increase subsequent risk of childhood asthma, and that the influence is stronger in children younger than 5 years old. Future research on the common immunological aberrancies of these disorders is warranted.

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Yu-Chiao Wang carried out the initial analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Chia-Hung Kao coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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