

Increased incidence of juvenile-onset systemic lupus erythematosus among children with asthma

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Abstract

Background: Children with systemic lupus erythematosus (SLE) have an especially aggressive disease course and poor outcomes. Previous studies demonstrated a possible association between SLE and allergies, but the relationship between these disorders remains unclear. This population-based cohort study aimed to investigate the incidence and risk of juvenile-onset SLE (JSLE) among children with asthma.

Methods: From 2000 to 2003, 120,939 children with newly diagnosed asthma and 483,756 randomly selected non-asthma controls were enrolled. We used a multivariable Cox proportional hazard regression model to measure and compare the incidence rate and risk of JSLE in the asthma and non-asthma cohorts.

Results: The overall incidence of JSLE was 2.52 times greater in the asthma cohort than that in the non-asthma cohort [3.49 vs. 1.53 per 100,000 person-years; 95% confidence interval (CI): 1.59–3.99]. The risk of JSLE was greatest among boys [hazard ratio (HR) 3.02, 95% CI: 1.21–7.52] and children aged 6–10 yr (HR 3.50, 95% CI: 1.75–7.02). The HR of JSLE increased with greater frequency of asthma-related medical visits from 1.22 (95% CI: 0.67–1.41) for those with ≤ 2 visits/yr to 5.88 (95% CI: 3.43–10.1) for subjects with > 2 visits/yr (trend test $p < 0.001$). However, the risk of JSLE declined over time.

Conclusion: We found an increased incidence of JSLE among children with asthma. The mechanism of asthma on JSLE development should be elucidated to establish innovative disease intervention programs.

Systemic lupus erythematosus (SLE) is a severe, multisystemic autoimmune disease, characterized by autoantibody overproduction, accumulation of immune complexes, and subsequent organ damage (1, 2). Up to 20% of patients with SLE experience onset during childhood (3, 4). Children with SLE have more serious organ involvement, more aggressive disease course, and worse outcomes (3, 4). The annual incidence of juvenile-onset SLE (JSLE) is < 1 per 100,000 children per year, and the low incidence makes it a challenge to conduct a study

with a substantial number of patients (5). To date, there is no screening diagnostic tool for preventing SLE nor is there a cure for the disease. Long-term immunosuppressive therapy with multiple adverse effects is still the mainstay of treatment. Although great efforts have been taken toward better understanding and developing treatment strategies for SLE over the past 60 yr, the etiology of SLE has not clearly established (1, 2).

Previous studies have described the association between SLE and allergic diseases, but their results have been somewhat controversial (6–10). Recently, studies reported an association between increased serum IgE in patients with SLE and disease activity (11–16). Allergic disorders, such as asthma, are

Abbreviations

SLE, Systemic lupus erythematosus; JSLE, Juvenile-onset systemic lupus erythematosus; Th1, T helper1 cells; Th2, T helper2 cells.

considered T-helper type 2 (Th2)-related immune responses with IgE-mediated inflammation at sites of persistent or repetitive exposure to allergens (17). In contrast, other research considers SLE a T-helper type 1 (Th1)-related immune response with the expansion of autoreactive T and B cells and autoantibody production and immune complex deposition at sites of the involved system (1, 2). Whether the Th1-related allergic diseases contribute to the development of Th1-related autoimmune disease remains unknown.

Asthma is on the rise worldwide, and there is increasing interest on the long-term health consequences of this disease. In addition, human epidemiological studies that explore the causal associations between asthma and JSLE in children are lacking. Therefore, we performed a population-based cohort study to examine a potential causal association between childhood asthma and JSLE.

Methods

Data sources

Taiwan's National Health Insurance (NHI), a single-payer, social insurance plan that requires only minimal copayment fees, covers 99% of the population, and the Bureau of NHI (BNHI) contracts with 99% of hospitals in Taiwan (18, 19). NHI also provides datasets for research related to cost, quality of health services, medical practice patterns, accessibility to health care programs, and treatment outcomes at the national and local levels (<http://www.nhi.gov.tw/english/index.aspx>) (18, 19). This study used a random sample of half of all children insured through the NHI.

This study was exempt from the Institutional Review Board because the National Health Insurance Research Database (NHIRD) contains de-identified information, and data are publicly available through an application process.

The ICD-9 diagnostic codes are accurate and a valid tool for identifying patients with specific diseases using data from the NHIRD database (20, 21).

Study design and subjects

Subjects in our asthma cohort included 120,939 patients aged 1–18 yr with a new diagnosis of asthma (ICD-9-CM codes 493 and 494) from 2000 to 2003. For each child with asthma, we randomly selected four children free of asthma (483,756 children) and were frequency matched by sociodemographic factors [sex, age (± 1 yr), urbanization of residential area, and parental occupation] and baseline year. To improve diagnostic accuracy, only subjects with three or more consecutive diagnoses of asthma could be designated as having asthma. The date of asthma diagnosis was defined as the index date used to initiate follow-up for calculating the person-years.

Children with asthma who were diagnosed with JSLE before the index dates were excluded. JSLE diagnosis based on ICD-9 code was also confirmed using the Registry for Catastrophic Illness Patient Database (RCIPD), which includes data on selected major injuries or illnesses and is published by the Department of Health, Executive Yuan, Taiwan. To register

JSLE in the RCIPD, a diagnosis must be made by a board-certified specialist and the application is further reviewed and approved by the Bureau of NHI, ensuring an accurate and reliable diagnosis. Each subject was monitored from the index date until a new diagnosis of JSLE was established, until withdrawal from the insurance program, until death, or until the end of follow-up on December 31, 2008, whichever occurred first.

Statistical analysis

Socio-demographic variables measured in this study were sex, age, urbanization, and parents' occupation. City districts and townships where subjects were registered for insurance purposes were grouped into four levels of urbanization based on population density (residents/km²): Level 1 indicates the most urbanized area and level 4 indicates the least urbanized area.

We first compared the demographic characteristics between the asthma cohort and the non-asthma cohort using a chi-square test. Then, we calculated the overall incidence of JSLE and incidence stratified by age and sex for each cohort. Univariable and multivariable Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of JSLE for the asthma cohort compared to the asthma-free cohort.

We also used the Cox model to estimate the HR of JSLE between the two cohorts, stratified by the average number of asthma-related medical visits per year. The average asthma-related medical visits per year were 2; thus, we used two as a cutoff to analyze the risk of JSLE. Additionally, we assessed the role of asthma duration on the risk of JSLE using time-dependent covariates. The cutoffs for asthma duration were equally divided every 3 yr (≤ 3 , 4–6, and > 6 yr since asthma diagnosis).

The study used the SAS software (version 9.2 for windows; SAS Institute Inc., Cary, NC, USA) for all data analyses.

Results

We enrolled 120,939 subjects in the asthma cohort and 483,756 subjects in the asthma-free cohort. Demographic characteristics are shown in Table 1. Mean ages (standard deviations) were 4.36 (3.44) yr and 4.61 (3.68) yr for the asthma and non-asthma cohorts, respectively. More than half of the children with asthma were ≤ 5 yr of age and 60.3% were boys. Patients with asthma were more likely to reside in urban areas (59.9%) and have parents with white-collar occupations (64.0%).

The overall incidence of JSLE was higher in the asthma cohort than in the non-asthma cohort (3.49 vs. 1.53 per 100,000 person-years) (Table 2). The Cox proportional hazard regression model revealed that children with asthma were 2.52 times as likely to develop JSLE (95% CI: 1.59–3.99) after controlling for age. Children aged 6–10 yr with asthma had the greatest risk of JSLE (adjusted HR 3.50, 95% CI: 1.75–7.02). The risk of JSLE was significantly increased for children with asthma regardless of sex (adjusted HR 3.02, 95% CI: 1.21–7.52 for boys; and adjusted HR 2.36, 95% CI: 1.39–4.03 for girls).

The association between the average number of medical visits because of asthma and SLE development was measured

Table 1 Comparisons of demographic characteristics between children with asthma and non-asthma controls

	Non-asthma (n = 483,756) n (%)	Asthma (n = 120,939) n (%)	p-value
Age (yr), mean $\pm$ s.d.	4.61 $\pm$ 3.7	4.36 $\pm$ 3.4	<0.001
Age			
≤ 5	329,356 (68.1)	82,339 (68.1)	<0.99
6–10	114,051 (23.6)	25,813 (23.6)	
>10	40,348 (8.34)	10,087 (8.34)	
Sex			
Male	291,532 (60.3)	72,883 (60.3)	<0.99
Female	192,224 (39.7)	48,056 (39.7)	
Follow-up time (yr) mean $\pm$ s.d.	7.04 $\pm$ 1.31	7.12 $\pm$ 1.21	<0.001
Urbanization*			
1	141,104 (29.4)	35,276 (29.4)	<0.99
2	146,396 (30.5)	36,599 (30.5)	
3	87,272 (18.2)	21,818 (18.2)	
4	106,060 (22.1)	26,515 (22.1)	
Parent's occupation			
White collar	309,396 (64.0)	77,349 (64.0)	<0.99
Blue collar	123,952 (25.6)	30,988 (25.6)	
Others†	50,408 (10.4)	12,602 (10.4)	

Chi-square test.

*The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized.

†Other occupations included primarily retired, unemployed, or low income populations.

using the average annual frequency (Table 3). Overall, the risk of JSLE increased from 1.22 in children with ≤ 2 visits to 5.88 in children with >2 visits (trend test $p < 0.0001$). The risk was similar for both sexes.

During the first 3 yr after asthma diagnosis, the incidence rate of JSLE was greater among asthmatic children than among non-asthmatic children (3.59 vs. 1.11 per 100,000

person-years), with an adjusted HR of 3.55 (95% CI: 1.66–7.60) (Table 4). A similar result was also noted in those with 4–6 yr of follow-up for their asthma.

Discussion

To our knowledge, this is the first population-based cohort study to investigate the incidence of JSLE among children with and without asthma. The results show a significantly increased incidence rate of JSLE among subjects with asthma regardless of sex. During the first 6 yr after asthma diagnosis, physicians should pay close attention to the expression of JSLE-related biomarkers.

Juvenile-onset SLE is a rare disease with an estimated annual incidence of 0.36–0.9 per 100,000 children per year, with a significantly higher incidence among non-Caucasian children, especially Asians and African Americans (5, 22). The current study revealed an incidence rate of 1.5 per 100,000 person-years among non-asthmatic Han Chinese children. Interestingly, we observed a significantly higher incidence rate of JSLE (3.49 per 100,000 persons per year) among asthmatic children. In addition, the incidence rate was higher in children with asthma older than 8 yr of age (11.95 per 100,000 person per year) and girls (6.16 per 100,000 person per year). The observed higher incidence rate of JSLE among children with more asthma-related medical visits may indicate that the risk of JSLE increases with more serious or uncontrolled airway inflammation due to asthma.

It is well recognized that the pathogenesis of JSLE involves the loss of self-tolerance due to environmental and/or genetic factors (1). It is evident that these factors contribute to the development and/or severity of disease but their roles are poorly understood. There are only a few studies, all with small sample sizes, investigating the association between allergic diseases and JSLE, and these studies produced inconsistent results (6–9). Furthermore, most of these studies were cross-sectional in nature, mainly focusing on adult patients (6–9). The causality between allergic disease and JSLE in children has not been clearly established.

Table 2 The incidence rate and risk of systemic lupus erythematosus (SLE) in children with asthma and non-asthma controls, stratified by age and gender

	Non-asthma			Asthma			Crude HR (95% CI)	Adjusted HR† (95% CI)
	SLE case	Person-years	IR	SLE case	Person-years	IR		
All	52	3,408,193	1.53	30	860,628	3.49	2.28 (1.45, 3.57)***	2.52 (1.59, 3.99)***
Age								
≤ 5	16	2,303,887	0.69	5	582,405	0.86	1.22 (0.45, 3.33)	1.30 (0.47, 3.58)
6–10	18	815,172	2.21	16	205,642	7.78	3.53 (1.80, 6.92)***	3.50 (1.75, 7.02)***
>10	18	288,381	6.24	9	72,581	12.40	2.00 (0.90, 4.44)	2.11 (0.94, 4.74)
Sex								
Male	11	2,057,607	0.53	9	519,527	1.73	3.24 (1.34, 7.81)**	3.02 (1.21, 7.52)*
Female	41	1,350,586	3.04	21	341,101	6.16	2.02 (1.19, 3.42)**	2.36 (1.39, 4.03)**

IR, incidence rate, per 100,000 person-years; HR, hazard ratio.

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

†Adjusted for age.

Table 3 The incidence rate and risk of systemic lupus erythematosus (SLE) in children with asthma, stratified by frequency of annual medical visits and sex

Frequency, per years	SLE case	Person-years	IR	Crude HR (95% CI)	Adjusted HR† (95% CI)
All					
None	52	3,407,440	1.53	1.00	1.00
≤2	10	534,894	1.87	1.20 (0.61, 2.35)	1.22 (0.62, 2.40)
>2	20	325,734	6.14	4.16 (2.48, 6.97) ***	5.88 (3.43, 10.1) ***
p for trend				<0.001	<0.001
Male					
None	11	2,056,854	0.53	1.00	1.00
≤2	4	314,959	1.27	2.29 (0.73, 7.19)	2.27 (0.72, 7.12)
>2	5	204,568	2.44	4.83 (1.68, 13.9)	4.56 (1.43, 14.5)*
p for trend				0.003	0.007
Female					
None	41	1,350,586	3.04	1.00	1.00
≤2	6	219,935	2.73	0.88 (0.37, 2.07)	0.93(0.39, 2.20)
>2	15	121,165	12.4	4.20 (2.32, 7.59)***	6.33 (3.44, 11.6)***
p for trend				<0.001	<0.001

IR, incidence rate, per 100,000 person-years; HR, hazard ratio.

*p < 0.05, **p < 0.01, ***p < 0.001.

†Adjusted for age.

Table 4 The incidence rate and risk of systemic lupus erythematosus (SLE) in children with asthma, stratified by follow-up years

Follow time (yr)	Non-asthma			Asthma			cHR (95% CI)	aHR† (95% CI)
	SLE case	Person-years	IR	SLE case	Person-years	IR		
≤3	16	1,443,281	1.11	13	362,527	3.59	3.24 (1.56, 6.73)**	3.55 (1.66, 7.60)**
4–6	15	1,378,414	1.09	8	348,257	2.30	2.11 (0.90, 4.98)	2.46 (1.03, 5.86)*
>6	21	585,746	3.59	9	149,844	6.01	1.67 (0.77, 3.65)	1.82 (0.83, 4.01)

IR, incidence rate, per 100,000 person-years; HR, hazard ratio.

*p < 0.05, **p < 0.01.

†Adjusted for age.

There are many strengths of our study. First, this is the first cohort study to quantify the incidence of JSLE among children with asthma. Our results, contrary to the Th1/Th2 paradigm (23–25), revealed a higher incidence rate and risk of JSLE in children with asthma and a higher risk of JSLE with increasing severity of asthma symptoms. Second, the current study is a population-based study, which minimizes selection bias typically relevant in case–control study designs. Third, JSLE was defined using ICD-9-CM and RCPD, which supports the validity of our diagnosis classification. The physician-diagnosed asthma minimizes selection bias and recall bias. Fourth, we adjusted for numerous possible confounding factors, including age, sex, urbanization of residence area, parental occupation, and baseline year.

Our findings suggest that asthma may influence the development of JSLE and that the two diseases may share common determinants. Our findings may also explain the rising incidence of allergic diseases and autoimmune diseases in epidemiological evidence (24). Inflammation due to hyper-responsiveness to allergens is an immunological characteristic of asthma; similar responses to antigens, such as drugs and

opportunistic infections, have been observed in patients with JSLE (26). Studies show increased activity of Th2-related cytokines [interleukin (IL)-4, IL-5, IL-6, and IL-10] between both patient groups (27). Decreased consumption of homeostatic factors and immunoregulation, such as regulatory T cell subsets and Toll-like receptor may be involved in the underlying mechanisms of allergy and autoimmune disease (24). In addition, autoimmune and allergic diseases may share genetic predisposition or genes that interact with shared environmental risk factors (24, 28). Therefore, immunogenetic factors and early-life environmental factors may both contribute to the development of asthma and JSLE.

Increased total serum IgE has also been described in patients with JSLE (11–16). Some studies suggest that increased IgE correlates with disease activity and nephritis (11, 12, 14). A recent study, using both a mouse model and human subjects, reported that the activation of the basophil by autoreactive IgE-containing immune complexes amplifies the production of autoantibodies and contributes to the pathogenesis of disease (15, 16). This research supports our finding of a Th2 environment in contributing to the development of JSLE.

There are several limitations to this study. Follow-up lasted about 10 yr, which may not be long enough to observe an association between asthma and JSLE. However, we still observed a prominent association between asthma and JSLE. Even though the current study is the largest population to investigate the incidence of JSLE in an asthma cohort, JSLE is a very rare disease and subsequent risk analysis of more frequently occurring presentations of JSLE, such as lupus nephritis, thrombocytopenia, and encephalopathy, cannot be performed due to insufficient patient numbers. In addition, a number of possible confounding variables between asthma and JSLE (e.g., body mass index, serum IgE level, and family history of allergic diseases) were not included in our database. Furthermore, there was a lack of data on genetic and behavioral factors that may affect the risk of JSLE and allergic diseases. Lastly, the population of this study is Chinese and may not be generalized to other populations.

In conclusion, this population-based cohort study revealed a significantly increased incidence rate of JSLE in children with asthma regardless of sex. Future research should explore the role of Th2-mediated allergic disease in the development of Th1-mediated autoimmune disease and provide a potential strategy of diagnosis and therapeutic promise in disease intervention.

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The authors have indicated that they have no financial relationships relevant to this article to disclose.

Conflict of interest

None.

Authors contribution

Chang-Ching Wei, Te-Chun Shen and Jeng-Dau Tsai conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Cheng-Li Lin and Tsai-Chung Li carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. Chi-Jung Chung coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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