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Original Contribution

Association of Scrub Typhus With the Risk of Autoimmune Diseases: A Population-Based Cohort Study

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Infection plays a major role in the development of autoimmune diseases. In this study, we investigated the relationship between scrub typhus and systemic autoimmune diseases. We enrolled 6,928 hospitalized patients with scrub typhus between 2000 and 2012 from the Taiwan National Health Insurance Research Database, and we compared them with 27,712 selected inpatients who had never been diagnosed with scrub typhus (1:4 ratio, matched by age, sex, and index year) in relation to the risk of developing autoimmune diseases. Cox proportional hazards regression analysis was used to analyze the risk of autoimmune diseases by sex, age, and comorbidities, with hazard ratios and 95% confidence intervals. The adjusted hazard ratio for autoimmune diseases for the scrub typhus group was 2.4 (95% confidence interval: 1.66, 3.48, $P < 0.0001$) compared with the control group. Subgroup analysis showed that women aged <40 years had a significant higher risk of autoimmune diseases. The risk was significantly higher within 3 years after scrub typhus infection. In conclusion, a higher risk of autoimmune diseases was found among the scrub typhus group, especially for female patients, those aged <40 years, and within the first 3 years after getting scrub typhus.

autoimmune diseases; cohort study; scrub typhus

Abbreviations: CI, confidence interval; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NHI, National Health Insurance; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Autoimmune diseases are a leading cause of mortality in young and middle-aged women in the United States (1, 2). Systemic autoimmune diseases are characterized by dysregulation of the immune system, which in turn activates the immune cells to attack autoantigens, resulting in inappropriate inflammation and multitissue damage. Autoimmune diseases range from the common rheumatoid arthritis (RA), Sjögren syndrome, and systemic lupus erythematosus (SLE) to the relatively rare systemic sclerosis, polymyositis, and dermatomyositis (3). The mechanism of pathogenesis of systemic autoimmune diseases is unclear; however, genetic factors, infections, endocrine disorders, and environmental exposure are thought to be involved (4–6). Of the environmental factors, infections play a major role in the development of autoimmune diseases, and viruses, bacteria, and other infectious pathogens are considered to be major triggers of autoimmunity (7).

The incidence of rickettsiosis, a disease caused by intracellular bacteria, has increased due to global warming. Rickettsioses are zoonotic infections caused by obligate intracellular bacteria of the genera *Rickettsia* and *Orientia*, belonging to the family *Rickettsiaceae* (8, 9). Rickettsioses caused by different strains have similar clinical symptoms, such as fever, headache, myalgia, cough, maculopapular/petechial rash, nausea, pharyngitis, lymphadenopathy, and eschar without pathognomonic signs. Scrub typhus, also known as tsutsugamushi disease, is an acute febrile infectious illness that is caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*. It is transmitted to humans and rodents by some species of trombiculid mites. The clinical picture of scrub typhus typically presents high fever, chill, myalgia, headache, and a maculopapular rash with eschar formation (10, 11). The clinical course of scrub typhus is usually mild and self-limiting, with the patient spontaneously

recovering after a few days. However, scrub typhus, especially in misdiagnosed/delayed-diagnosis cases, might progress into multiorgan failure, among which acute kidney injury, acute respiratory distress syndrome, myocarditis, hemophagocytic lymphohistiocytosis, and meningitis have been reported (12, 13).

The association of rickettsiosis and autoimmune diseases has yet to be determined. Pedro-Botet et al. (14) reported that patients with Mediterranean spotted fever disease caused by *R. conorii* had arthritis in large joints with joint effusion in the hips, knees, and ankles. Pappas et al. (15) also reported that *Coxiella burnetii* can induce reactive arthritis. In addition, Rocky Mountain spotted fever, a life-threatening tick-borne illness caused by *R. ricketsii*, has also been proposed to be associated with polyarticular arthritis (16). A previous epidemiologic study showed that *R. marmionii* was associated with chronic illness in 14 patients with rickettsioses. Of these 14 patients, 8 had autoimmune disease including RA, Hashimoto thyroiditis, and polymyalgia rheumatica (17). As an endemic area for scrub typhus, Taiwan has a high standardized incidence ratio in the less-developed, mountainous areas in the central and eastern regions of the country (18). Due to a lack of research on the epidemiologic relationship between scrub typhus and the subsequent development of autoimmune diseases, this longitudinal nationwide cohort study was conducted to explore whether patients with scrub typhus are prone to the subsequent development of RA, SLE, Sjögren syndrome, polymyositis, dermatomyositis, and systemic scleroderma.

METHODS

Data source

The data used in this study were from the Taiwan National Health Insurance Research database, released by the National Research Institutes for research purposes. The Taiwan National Health Insurance (NHI) program was established in 1995, and currently covers over 99% of the population in Taiwan (19). Data in the Health Insurance Research database includes inpatient expenditure by admission and the inpatient records of all beneficiaries enrolled in the NHI program. We also used the database of catastrophic illnesses. For patient privacy, identity is encrypted before being released by the National Research Institutes. This study was approved by the institutional review board and the hospital research ethics committee of China Medical University (institutional review board permit CMUH-104-REC2-115).

Study subjects

The subjects in this study were hospitalized patients infected with scrub typhus (*International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) codes 081.0, 081.2, and 081.9) during 2000–2013. The index date was defined as the date of a diagnosis of scrub typhus. Patients with a diagnosis of the following diseases were excluded: autoimmune diseases (RA: ICD-9-CM code 714; SLE: ICD-9-CM code 710.0; Sjögren syndrome: ICD-9-CM code 710.2; systemic sclerosis: ICD-9-CM code 710.1; polymyositis: ICD-9-CM code 710.3; and dermatomyositis: ICD-9-CM code 710.4). Those who withdrew from the NHI program before the index date were also excluded. The comparison group was selected from inpatients who had never been diagnosed with scrub typhus at a ratio of 1:4 to the scrub typhus group and matched by age, sex, and index year.

Outcome and relevant variables

All of the autoimmune diseases included in this study (RA, SLE, Sjögren syndrome, systemic sclerosis, polymyositis, and dermatomyositis) are classified as catastrophic illnesses in Taiwan. The patients were followed until a diagnosis of an autoimmune disease, withdrawal from the NHI program, or the end of 2013, whichever occurred first. The comorbidities analyzed in this study were hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496), asthma (ICD-9-CM code 493), cancer (ICD-9-CM codes 140–208), allergic rhinitis (ICD-9-CM codes 477 and 472.0), atopic dermatitis (ICD-9-CM code 691), chronic liver diseases (ICD-9-CM code 571.4), hepatitis B (ICD-9-CM codes 070.2, 070.3, and V02.61), and hepatitis C (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, and V02.62).

Statistical analysis

Table 1 shows comparisons of the demographic data of the case and control groups using the χ^2 test for category variables and *t* test for continuous variables. We calculated person-years from the sum of the follow-up time for each individual, and the follow-up time was defined as the period from the index date to the diagnosis of an autoimmune disease, withdrawal from the NHI program, or the end of 2013. The incidence rate was calculated according to the number of occurrences and person-years. Hazard ratios and 95% confidence intervals for the 2 groups were estimated using univariate and multivariate Cox proportional hazard regression models. The variables in the multivariate model included age, sex, and all comorbidities. The Kaplan-Meier method was used to describe the cumulative incidence of autoimmune diseases among the groups; differences between the groups were evaluated using the log rank test. SAS, version 9.4 for Windows (SAS Institute Inc., Cary, North Carolina), was used for data analysis, and a *P* value less than 0.05 was considered to indicate statistical significance.

RESULTS

Demographic characteristics and comorbidities

The eligible study participants included 6,928 patients in the scrub typhus group and 27,712 patients in the comparison group. The hospitalization diagnoses for the controls were diverse. The main diagnoses were gastrointestinal disorders (e.g., gastroenteritis, appendicitis, hernia, hemorrhoids), traumatic injuries, genitourinary disorders (e.g., urinary tract infection, urolithiasis, chronic renal failure), cardiovascular disorders (e.g., coronary heart disease), pulmonary disorders (e.g., pneumonia, airway diseases), and

Table 1. Baseline Characteristics of a Population-Based Cohort Study of Associations of Scrub Typhus With the Risk of Autoimmune Diseases, Taiwan, 2000–2013

Characteristic	Scrub Typhus Status				*P* Value
	Yes (n = 6,928)		No (n = 27,712)		
	No.	%	No.	%	
Sex					1.00
Male	4,460	64.4	17,840	64.4	
Female	2,468	35.6	9,872	35.6	
Age group, years[a]					1.00
≤19	680	9.82	2,720	9.82	
20–39	2,328	33.6	9,312	33.6	
40–64	2,906	41.9	11,624	41.9	
≥65	1,014	14.6	4,056	14.6	
Comorbidity					
Hypertension	931	13.4	3,489	12.60	0.06
Diabetes mellitus	646	9.32	2,183	7.88	<0.0001
Hyperlipidemia	334	4.82	825	2.98	<0.0001
COPD	159	2.30	275	0.99	<0.0001
Asthma	165	2.38	262	0.95	<0.0001
Cancer	115	1.66	512	1.85	0.29
Allergic rhinitis	104	1.50	542	1.96	0.01
Atopic dermatitis	27	0.39	33	0.12	<0.0001
Chronic liver diseases	141	2.04	78	0.28	<0.0001
Hepatitis B	281	4.06	482	1.74	<0.0001
Hepatitis C	127	1.83	181	0.65	<0.0001

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

[a]Age data expressed by mean: scrub typhus group: 43.5 (SD, 19.3); control group: 43.5 (SD, 19.3), $P = 0.99$.

orthopedic disorders (e.g., osteoarthritis and herniated intervertebral disc) (Table 2). There were no significant differences in age and sex between the 2 groups. There were more male patients than female, and most of the patients were aged 20–64 years. The scrub typhus group had a higher incidence rate of comorbidities except for cancer and hypertension. The mean follow-up times in the scrub typhus and comparison groups were 6.06 and 5.97 years, respectively.

Table 2. Main Diagnoses for Hospitalizations for Controls in a Population-Based Cohort Study of Associations of Scrub Typhus With the Risk of Autoimmune Diseases, Taiwan, 2000–2013

Diagnosis Category	No. of Cases (n = 27,712)	%[a]
Traumatic injuries	5,673	20.5
Gastrointestinal disorders	4,033	14.6
Pulmonary disorders	3,069	11.1
Cardiovascular disorders	2,880	10.4
Genitourinary disorders	1,925	6.9
Orthopedic disorders	867	3.1

[a] Percentage of all inpatient controls.

Comparison of the incidence and hazard ratios for autoimmune diseases was stratified by sex and age of the patients with scrub typhus and the comparison cohort.

The incidence rates of autoimmune diseases in the scrub typhus and comparison groups were 11.0 and 4.6 per 10,000 person-years, respectively. Compared with the control group, the adjusted hazard ratio for autoimmune diseases for the scrub typhus group was 2.4 (95% confidence interval (CI): 1.66, 3.48) (Table 3). The survival curve (Figure 1) showed that the cumulative incidence of autoimmune diseases was higher in the scrub typhus group than in the comparison group ($P < 0.0001$). Compared with women without scrub typhus, women with scrub typhus had a 2.94-fold higher risk of autoimmune diseases (95% CI: 1.93, 4.50) (Table 4). In age-subgroup analysis, the scrub typhus group had an increased risk of autoimmune diseases in two age groups (for ages ≤19 years, adjusted hazard ratio = 30.3, 95% CI: 3.75, 245; for ages 20–39 years, adjusted hazard ratio = 2.47, 95% CI: 1.25, 4.88). In the comorbidities-subgroup analysis, among patients without any comorbidities, the scrub typhus group had a significant, higher risk of autoimmune diseases. (adjusted hazard ratio = 2.33, 95% CI: 1.54, 3.54); among patients with comorbidities, the scrub typhus group also had a significant, higher risk of autoimmune diseases. (adjusted hazard ratio = 2.68, 95% CI: 1.18, 6.10)

In order to clarify the causes of autoimmune arthritis, we analyzed the risk of each autoimmune disease (Table 5). Compared with the control group, the scrub typhus group had a 6.44-fold higher risk of SLE (95% CI: 2.78, 14.9) and a 2.19-fold higher risk of Sjögren syndrome (95% CI: 1.18, 4.07).

Risk of autoimmune diseases according to follow-up time

Table 6 shows the incidence and hazard ratios of autoimmune diseases stratified by follow-up time. The incidence rates of autoimmune diseases were the highest and most significant in the first 3 years at 16.5 and 5.91 per 10,000 person-years in the scrub typhus and comparison groups, respectively. A significant, 2.88-fold increase in the risk of developing autoimmune diseases was observed within the first 3 years of follow-up (95% CI: 1.78, 4.65).

DISCUSSION

In this nationwide population-based cohort study, we found that, in comparison with the general population, patients with scrub typhus had a 2.4-fold higher incidence of autoimmune diseases. Furthermore, the association of scrub typhus with autoimmune diseases was found to be more significant in female patients and those aged <40 years. A prominent risk (2.88-fold) of developing autoimmune diseases was also observed in the first 3 years after a diagnosis of scrub typhus, when compared with the general population. Although patients with scrub typhus had a significantly higher rate of comorbid disease than those in the control group, scrub typhus

Table 3. Incidence and Hazard Ratios for Autoimmune Diseases, Comparing Patients With or Without Scrub Typhus in a Population-Based Cohort Study of Associations of Scrub Typhus With the Risk of Autoimmune Diseases, Taiwan, 2000–2013

Variable	No. of Events	No. of Person-Years	IR per 10,000 Person-Years	Crude Analysis			Adjusted Analysis[a]		
				HR	95% CI	*P* Value	HR	95% CI	*P* Value
Scrub typhus									
No	76	16,5325	4.60	1.00	Referent		1.00	Referent	
Yes	46	42,009	11.0	2.38	1.65, 3.44	<0.0001	2.4	1.66, 3.48	<0.0001
Sex									
Male	32	135,137	2.37	1.00	Referent		1.00	Referent	
Female	90	72,197	12.47	5.21	3.48, 7.8	<0.0001	5.02	3.33, 7.55	<0.0001
Age group, years									
≤19	9	23,421	3.84	1.00	Referent		1.00	Referent	
20–39	36	77,589	4.64	1.19	0.58, 2.48	0.63	1.51	0.72, 3.16	0.27
40–64	57	82,584	6.90	1.69	0.84, 3.42	0.14	1.67	0.82, 3.43	0.16
≥65	20	23,740	8.42	1.95	0.89, 0.29	0.10	2.01	0.89, 4.56	0.09

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a] Model adjusted for sex, age, and all comorbidities listed in Table 1.

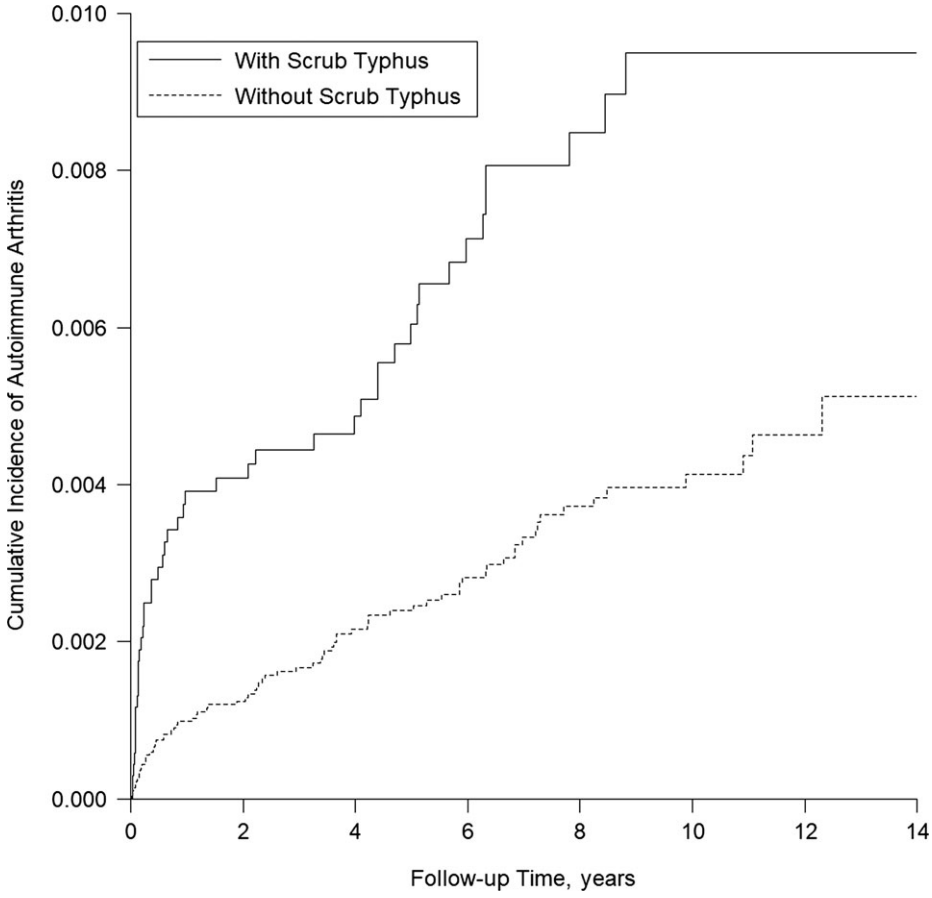

Figure 1. The cumulative incidence of autoimmune diseases for patients with and without scrub typhus, Taiwan, 2000–2013 ($P < 0.0001$).

Table 4. Incidence and Hazard Ratios for Autoimmune Diseases Among Patients Stratified by Sex, Age, and Comorbidity in a Population-Based Cohort Study of Associations of Scrub Typhus With the Risk of Autoimmune Diseases, Taiwan, 2000–2013

Variable	Scrub Typhus Status						Risk of Autoimmune Disease					
	Yes			No			Crude Analysis			Adjusted Analysis[a]		
	No. of Events	No. of Person-Years	IR per 10,000 Person-Years	No. of Events	No. of Person-Years	IR per 10,000 Person-Years	HR	95% CI	No. of Events	HR	95% CI	No. of Events
Overall	46	42,009	11.0	76	165,325	4.60	2.38	1.65, 3.44	<0.0001	2.40	1.66, 3.48	<0.0001
Sex												
Male	8	27,676	2.89	24	107,461	2.23	1.30	0.58, 2.88	0.53	1.27	0.57, 2.85	0.56
Female	38	14,333	26.5	52	57,864	8.99	2.94	1.93, 4.46	<0.0001	2.94	1.93, 4.50	<0.0001
Age group, years												
≤19	8	4,615	17.3	1	18,806	0.53	32.1	4.01, 257	0.001	30.3	3.75, 245	0.001
20–39	14	15,518	9.02	22	62,072	3.54	2.54	1.30, 4.97	0.01	2.47	1.25, 4.88	0.01
40–64	18	16,801	10.7	39	65,783	5.93	1.81	1.04, 3.16	0.04	1.73	0.98, 3.06	0.06
≥65	6	5,075	11.8	14	18,665	7.50	1.60	0.61, 4.16	0.92	1.78	0.68, 4.66	0.24
Comorbidity[b]												
No	34	31,342	10.8	63	131,129	4.80	2.26	1.49, 3.43	0.00	2.33	1.54, 3.54	<0.0001
Yes	12	10,666	11.3	13	34,197	3.80	2.98	1.36, 6.54	0.006	2.68	1.18, 6.10	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a] Model adjusted for sex, age, and all comorbidities listed in Table 1.
[b] Comorbidity: patients with any of the comorbidities listed in Table 1.

remained an independent risk factor for developing autoimmune arthritis in terms of sex, age, and comorbidities.

Systemic autoimmune diseases were selected for this study because they are defined as being catastrophic illnesses in Taiwan. The diagnoses are thus reliable, because the patients issued with a catastrophic illness certificate are exempted from copayments. To this end, the Bureau of NHI performs routine validation of the diagnoses by experienced rheumatologists who carefully review the original medical records, laboratory data, imaging findings, and pathological findings of all patients who apply for a catastrophic illness certificate. The Bureau of NHI issues catastrophic illness certificates only to those who meet the classification criteria for major illnesses.

Table 5. Incidence and Hazard Ratios for Different Autoimmune Diseases in a Population-Based Cohort Study of Associations of Scrub Typhus With the Risk of Autoimmune Diseases, Taiwan, 2000–2013

Autoimmune Disease	Scrub Typhus Status						Risk of Autoimmune Disease					
	Yes			No			Crude Analysis			Adjusted Analysis[a]		
	No. of Events	No. of Person-Years	IR per 10,000 Person-Years	No. of Events	No. of Person-Years	IR per 10,000 Person-Years	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Rheumatoid arthritis	15	42,009	3.57	34	165,325	2.06	1.74	0.95, 3.19	0.07	1.79	0.97, 3.29	0.06
Systemic lupus erythematosus	15	42,009	3.57	9	165,325	0.54	6.60	2.89, 15.1	<0.0001	6.44	2.78, 14.9	<0.0001
Sjögren syndrome	16	42,009	3.81	29	165,325	1.75	2.17	1.18, 3.99	0.01	2.19	1.18, 4.07	0.01
Systemic sclerosis	0	42,009	0.00	1	165,325	0.06						
Polymyositis and dermatomyositis	0	42,009	0.00	3	165,325	0.18						

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a] Model adjusted for sex, age, and all comorbidities listed in Table 1.

Table 6. Incidence and Hazard Ratios for Autoimmune Diseases According to Follow-up Year in a Population-Based Cohort Study of Associations of Scrub Typhus With the Risk of Autoimmune Diseases, Taiwan, 2000–2013

Follow-up Time, years	Scrub Typhus Status						Risk of Autoimmune Disease					
	Yes			No			Crude Analysis			Adjusted Analysis[a]		
	No. of Events	No. of Person-Years	IR	No. of Events	No. of Person-Years	IR	HR	95% CI	*P* Value	HR	95% CI	*P* Value
<3	29	17,547	16.5	41	69,408	5.91	2.81	1.74, 4.52	<0.0001	2.88	1.78, 4.65	<0.0001
3–6	11	12,643	8.70	19	49,358	3.85	2.26	1.07, 4.74	0.03	2.17	1.02, 4.63	0.04
6–9	6	7,654	7.84	12	29,985	4.00	1.96	0.74, 5.22	0.18	1.91	0.71, 5.16	0.20
>9	0	4,165	0.00	4	16,575	2.41						

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a] Model adjusted for sex, age, and all comorbidities listed in Table 1.

Although multiple factors are thought to contribute to the development of autoimmune diseases, immunological studies on animal models of autoimmune diseases strongly suggest that infections account for the main environmental factors triggering human autoimmune diseases (20–22), despite the fact that as yet relevant data are sparse.

Rickettsiae are small obligate intracellular bacteria transmitted to humans by arthropod vectors, some species of which have been documented to be associated with polyarticular arthritis (14–16). The underlying mechanism by which scrub typhus increases the risk of developing autoimmune diseases is unclear.

T-helper cell 17 and interleukin-17 are known to play important roles in the clearance of extracellular bacterial and fungal infections. However, strong evidence also implicates the T-helper cell 17 lineage in several autoimmune and autoinflammatory disorders, including multiple sclerosis, psoriasis, spondyloarthritis, RA, Sjögren syndrome, inflammatory bowel disease, SLE, and asthma (23–25).

This nationwide cohort study was conducted under the hypothesis that the national database was adequate to analyze the relationship between systemic autoimmune diseases and scrub typhus. The subgroup of women with scrub typhus had a 2.94 -fold higher risk of autoimmune diseases (95% CI: 1.93, 4.50), which might be due to hormonal factors. However, further studies are needed to clarify this relationship. Sex hormones have been implicated in immune responses, with estrogens acting as enhancers at least of humoral immunity and androgens and progesterone (and glucocorticoids) being natural immune-suppressors. In particular, the cortisol circadian rhythm has been reported to be altered, at least in RA, and to be partially involved in sex hormone circadian synthesis and levels (26).

In age-subgroup analysis, those aged <40 years and with scrub typhus had an increased the risk of autoimmune diseases, which often occurred in the young and in middle-aged immune-competent subjects. This suggests that their immune reactions to infections, including scrub typhus, were more intense than those in the elderly. The oldest group had a lower prevalence of autoimmune diseases. An animal model has shown that T-helper cell 17 cytokines have an important role in the pathology of and in protective immunity against fatal *Rickettsia typhi* infection (24). In humans, it has been reported that there are interleukin-17-producing T cells in the joints of those with systemic juvenile arthritis, but there is a reciprocal relationship to regulatory T-cell numbers at the same time (27). In addition, reduced frequency of circulating T-regulatory cells has been noted as an important pathogenesis in active systemic juvenile idiopathic arthritis (28). Therefore, many autoimmune diseases can be rare in the elderly. A possible explanation for this is the expansion of many protective regulatory mechanisms highly characteristic in the elderly. Of note is the higher production of peripheral T-regulatory cells. (29). Many autoimmune diseases, especially lupus and ankylosing spondylitis, are diagnosed predominantly in youth and middle age. This might be due to imbalanced T-helper and regulatory cells.

We noted a substantial risk of developing autoimmune diseases in the first 3 years after a diagnosis of scrub typhus infection. This phenomenon was associated with infections that triggered inflammation and molecular mimicry. Therefore, clinicians should be aware of the increased risk of autoimmune diseases in patients with scrub typhus, and these patients should be educated and monitored.

Our study has three significant strengths. First, this is, to our knowledge, the first large cohort study to investigate the association between scrub typhus and the subsequent development of autoimmune diseases. Second, we performed concise subgroup analysis to illustrate interrelationships of sex and age. Third, the validity of our findings was enhanced with unbiased subject selection and strict criteria for the diagnosis of systemic autoimmune diseases.

We did not analyze reverse causality (i.e., whether immune response in autoimmune disease increases susceptibility to scrub typhus). The immune response in autoimmune disease might be diversified; use of drugs in the treatment of autoimmune diseases has increased opportunistic infections related to therapy, although disease itself and comorbidities can also be factors affecting susceptibility. Some opportunistic infections are more common and related to specific immunological deficits, such as biologic therapies and tuberculosis. In addition, herpes zoster is one of the most common opportunistic infections related to immunosuppression. However, to our knowledge, there have not been previous studies showing that autoimmune disease increases susceptibility to scrub typhus.

There are also several limitations with regard to the analysis of the results. First, the ICD-9-CM codes for the diagnoses of scrub typhus and systemic autoimmune diseases were based on administrative claims data recorded by physicians and hospitals rather than in a prospective clinical setting. Inaccuracy might have resulted in misclassification despite the fact that the Bureau of NHI uses an auditing mechanism to minimize diagnostic uncertainty and misclassification (30). In addition, the systemic autoimmune diseases in this study were strictly defined by the catastrophic illness database, thus yielding better diagnostic validity. Furthermore, scrub typhus is a reportable infectious disease in Taiwan, and physicians should conduct a serological test, the Wei-Felix test, or indirect immunofluorescence when reporting. Therefore, the diagnosis of scrub typhus for inpatients will be more strictly reported. However, the laboratory (e.g., serological testing) results were not available in the National Health Insurance Research database, which is a possible limitation. Second, data on body mass index, smoking, socioeconomic status, and family history were unavailable, and all of these are potential confounding factors. Consequently, further analysis in relation to these variables could not be conducted, although chronic obstructive pulmonary disease was used as a proxy variable for cigarette smoking, and has been used this way in previous studies (31, 32). The major clinical difference between scrub typhus and SLE is history of travel or insect bite (or animal contact history) and the characteristic painless eschar of scrub typhus. It is possible that early lupus was misdiagnosed as scrub typhus, but this possibility is very limited. Third, the results of this study might have been affected by medications such as anticonvulsants, antihypertensive drugs, and hormone replacement therapy. Finally, future studies should seek to generalize these results to non-Asian ethnic groups, due to ethnic and geographic differences in the incidence of specific autoimmune diseases (2), although our findings do suggest a possible pathogenesis of autoimmune diseases and could increase the understanding of these diseases and lead to better care of the affected patients.

In conclusion, in this 14-year population-based cohort study, we found a higher risk of autoimmune diseases in patients with scrub typhus, especially among women and those aged <40 years. The risk was prominent within the first 3 years after a diagnosis of scrub typhus. Future studies are required to clarify the underlying biological mechanisms of these associations. We recommend that clinicians be aware of the increased risk of systemic autoimmune diseases in patients with scrub typhus and provide appropriate monitoring for the high-risk groups (female patients, patients aged <40 years, and within the first 3 years of infection) in addition to treating scrub typhus.

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Conflict of interest: none declared.

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