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Effect of enterovirus infections on asthma in young children: A national cohort study

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Abstract

Background: We conducted a cohort study to determine the relationship between enterovirus (EV) infection and asthma.

Materials and methods: From the National Health Insurance Research Database of Taiwan, we identified patients who received a new diagnosis of asthma and concurrent treatment between January 2000 and December 2011 (EV cohort: n = 208 213; non-EV cohort: n = 208 213). Cox proportional hazards regression analysis was performed to determine and compare the adjusted hazard ratios (aHRs) of asthma between these 2 cohorts. Kaplan-Meier analysis was conducted to assess the differences in the cumulative incidence curves of asthma between the 2 cohorts.

Results: The overall aHR of asthma was 1.48-fold higher in the EV cohort than in the non-EV cohort (95% confidence interval = 1.45-1.50). The aHR of asthma was higher in the EV cohort than in the non-EV cohort, comprising children aged ≤5 years, regardless of sex, sociodemographic factors (urbanization level and parental occupation) or comorbidities. The risk of asthma was higher in 1-3, 4-6, 7-9 and 10-12 months (all $P < .001$), particularly in those with a higher frequency of admission (>5 per year).

Conclusion: The incidence of asthma was higher in the EV cohort than in the non-EV cohort, comprising children aged ≤5 years, regardless of sex, urbanization level, parental occupation or season. In particular, the risk of asthma was higher in children with a higher frequency of admission, even in the absence of atopy or other respiratory infections.

KEYWORDS
asthma, cohort study, enterovirus

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1 | INTRODUCTION

Enterovirus (EV) infections are systemic infections.[1] Iwasaki et al[2] reported low-Ab responses against EV, such as echovirus, in children aged 2-5 years presenting to hospitals with asthma exacerbations.[2] Mertz et al[3] also reported that EV68 is associated with asthma in children. These reports imply that EV may play a key role in allergic respiratory diseases such as asthma.[2]

The efficient clearance of a virus is orchestrated by antibodies and type 1 cytokine-producing T cells. However, the airway of asthmatic patients is abundant in type 2 cytokines but deficient in type 1 cytokines, thus often prolonging viral infection and causing asthma exacerbation.[4] EV71 infection is less likely to evoke a strong T helper cell 1 (Th1) response in young children, who likely lack high neutralizing antibody (NAb) titres, resulting in the ineffective control of viral replication. The presence of low NAb titres may also result in the antibody-dependent enhancement of EV71 replication.[5] Therefore, children with EV71 infection mainly exhibit Th2 responses to EV71, and this results in excessive airway inflammation, thus contributing to asthma development in children.[6] In a recent study, Smith-Norowitz et al[7] found increased specific EV71 IgE Ab responses in children with asthma; this finding indicates that EV71 infection may be an infectious trigger in asthma, consistent with the aforementioned reports.

Asthma symptoms may be triggered or worsened by certain events such as respiratory infections,[8] allergy-related disease (eg atopic dermatitis or allergy rhinitis),[9] parental occupation,[10] and changes or extremes in weather.[11] No study has comprehensively investigated the effect of EV infection on asthma in children and whether this effect changes with age and season. Therefore, we conducted this national cohort study to determine the relationship between EV infection and asthma.

2 | METHODS

2.1 | Data source

In this retrospective cohort study, we used the claims data of children aged ≤5 years, which included the data of one-half of all the insured children randomly sampled from all insured children in the National Health Insurance Research Database (NHIRD) of Taiwan between 1996 and 2012 (http://nhird.nhri.org.tw/en/index.html; accessed in 2015). In Taiwan, the single-payer National Health Insurance programme was launched in March 1995, and this programme currently covers 99% of the population of Taiwan (23.74 million enrollees). To ensure patient privacy, all medical records in the NHIRD are encrypted with unique identifiers before being released for research purposes. The medical records of children were evaluated on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

2.2 | Ethics statement

Personal information in the NHIRD is encrypted to ensure patient privacy, and researchers are provided with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was granted exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR2). The IRB also specifically waived the consent requirement.

2.3 | Data availability statement

The data set used in this study is maintained by the Ministry of Health and Welfare (MOHW) of Taiwan. The MOHW approves any application to access this data set. Thus, for requesting access, researchers must submit an application form to the MOHW. Please contact the staff of the MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance: MOHW Address: No. 488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are provided in this study.

2.4 | Study patients

Children aged ≤5 years who were diagnosed as having EV infection (ICD-9-CM codes 008.67, 047, 048, 074, 079.1 and 079.2) between 1 January 2000 and 31 December 2011 were identified from the NHIRD and included in the EV cohort. The data in the NHIRD are rigorously validated. In Taiwan, the laboratory surveillance system for

EV was established after the 1998 outbreak of EV-A71. This system includes more than 250 sentinel clinics and hospitals located nationwide.[12] In Taiwan, the diagnosis of EV is based on positive isolates of EVs from throat swabs, rectal swabs or cerebrospinal fluid; serologic assays; and clinical and laboratory definitions[13] in the hospital-based surveillance system. To avoid diagnosis bias in the physician-based system, each sentinel physician collects 2-5 throat swabs each week[12] from patients with herpangina or hand-foot-mouth disease (HAMD) within 3 days of disease onset,[12] even without the appearance of severe symptoms.[14] Therefore, EV diagnoses are coded according to the hospital-based and physician-based surveillance systems in Taiwan. Both the physician-based and hospital-based surveillance systems have been maintained simultaneously since 1998. This policy ensures the early detection of minimal symptoms of EV among infants and children.[15] This study included the mild-to-moderate form of EV infection (eg herpangina or HAMD [ICD-9-CM codes 0740 or 0743, respectively])[16] and the severe form of other EV infections (eg meningitis [ICD-9-CM code 047]; Table A1 in Appendix). The primary purpose of this retrospective cohort study was to evaluate the association between EV infection and asthma. Hence, we excluded children diagnosed as having asthma (ICD-9-CM code 493). The index date for children with EV infections was the date of the first EV infection-related medical visit. Children without EV infections and without a history of asthma before the index date were selected and included in the non-EV cohort. The children in the non-EV cohort were frequency matched to the children in the EV cohort by age, sex, urbanization level, parental occupation and index year. The baseline comorbidities were as follows: allergic rhinitis (AR; ICD-9-CM code 477), atopic dermatitis (AD; ICD-9-CM code 691.8),[17] acute respiratory infections (ARIs; ICD-9-CM codes 460-466), pneumonia and influenza (ICD-9-CM codes 480-488),[8] other diseases of the upper respiratory tract (ICD-9-CM codes 470-478),[8] rhinovirus infection (ICD-9-CM code 079.3)[18] and mycoplasma (ICD-9-CM code 041.81).[19]

2.5 | Statistical analysis

The distributions of sociodemographic factors, namely age, sex, urbanization level and parental occupation, were compared between the EV and non-EV cohorts. The differences were determined using the chi-square test. The significance of the differences in the mean ages and mean follow-up periods for both cohorts was measured using the Student's *t* test. The incidence rates (per 1000 person-years) of asthma were calculated for each cohort. Multivariable Cox proportional hazards regression was used to compare the risk of EV-associated asthma in both cohorts. The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox model. The multivariable models were simultaneously adjusted for age, sex, urbanization level, parental occupation and comorbidities (such as AR, AD, ARIs, pneumonia and influenza, rhinovirus infection and mycoplasma, as well as other diseases of the upper respiratory tract). We also estimated the risk of asthma by EV subtypes. The Kaplan-Meier method was used to plot the cumulative incidence of asthma, and a log-rank test was used to compare the 2 cohorts. All data were analysed using SAS for Windows (Version 9.4, SAS Institute Inc., Carey, NC, USA). P value <.05 was considered statistically significant.

3 | RESULTS

In total, 208 213 patients with EV infection were included in the EV cohort, and 208 213 controls were included in the non-EV cohort, who were frequency matched by age, sex, urbanization level[9] and parental occupation (Table 1). The mean ages of the EV and non-EV cohorts were 1.98 ± 1.15 and 2.00 ± 1.14 years, respectively. Most patients and controls were 1-3 years old (58.8% vs 60.8%). The EV cohort included a larger number of boys (52.7% vs 52.7%), residents of highly urbanized areas (57.4% vs 57.5%) and children with parents engaged in white-collar occupations (66.8% vs 66.3%) than the non-EV cohort did. The EV cohort had a higher prevalence of comorbidities such as ARIs ($P = .001$) than the non-EV cohort did. During the mean follow-up of 7.43 years for the EV cohort and 7.95 years for the non-EV cohort, the cumulative incidence of asthma was significantly higher in the EV cohort than in the non-EV cohort (Figure 1, log-rank test $P < .001$). The overall incidence of asthma was higher in the EV cohort than in the non-EV cohort (31.7 vs 21.1 per 1000 person-years; Table 2). After adjustment for age, sex, urbanization level, parental occupation and comorbidities (such as AR, AD, ARIs, pneumonia and influenza, rhinovirus infection and mycoplasma, as well as other diseases of the upper respiratory tract), the risk of asthma was 1.48-fold higher in the EV cohort than in the non-EV cohort (95% CI = 1.45-1.50). The adjusted HRs (aHRs) of asthma (EV cohort to non-EV cohort) were high for each status (including all age groups, sex, urbanization level, parental occupation and presence or absence of comorbidities; all $P < .001$; Table 2).

Compared with the non-EV cohort, the EV cohort exhibited a higher risk of asthma in different seasons for EV infections: 1-3 months (aHR = 1.54, 95% CI = 1.50-1.59), 4-6 months (aHR = 1.43, 95% CI = 1.41-1.46), 7-9 months (aHR = 1.51, 95% CI = 1.48-1.54) and 10-12 months (aHR = 1.49, 95% CI = 1.46-1.52) (Table 3).

TABLE 1 Demographic data of children with and without enterovirus (EV) infections

	Non-EV (N = 208 213)		EV (N = 208 213)		
	n	(%)	n	(%)	*P*-value
Age, years, mean (SD)[a]	2.00	(1.14)	1.98	(1.15)	.001
Stratified age, y					
<1	41 241	(19.8)	44 465	(21.4)	
1-3	126 671	(60.8)	122 472	(58.8)	
3-5	40 304	(19.4)	41 276	(19.8)	
Sex					
Girl	98 467	(47.3)	98 545	(47.3)	.81
Boy	109 746	(52.7)	109 668	(52.7)	
Urbanization level[b]					
1 (highest)	56 027	(26.9)	55 869	(26.8)	.94
2	63 805	(30.6)	63 786	(30.6)	
3	42 133	(20.2)	42 244	(20.3)	
4 (lowest)	46 248	(22.2)	46 314	(22.2)	
Parental occupation					
White collar	138 075	(66.3)	139 099	(66.8)	.003
Blue collar	42 805	(20.6)	42 130	(20.2)	
Others[c]	27 333	(13.1)	26 984	(13.0)	
Comorbidity					
Allergic rhinitis	16 168	(7.77)	16 050	(7.71)0	.49
Atopic dermatitis	7597	(3.65)	7624	(3.66)	.82
Acute respiratory infections	2 306 030	(99.0)	205 760	(98.8)	.001
Pneumonia and influenza	39 895	(19.2)	40 190	(19.3)	.25
Other diseases of upper respiratory tract	42 356	(20.3)	42 640	(20.5)	.27
Rhinovirus infection[d]	47	(0.02)	51	(0.02)	.69
Mycoplasma[d]	9	(0.00)	8	(0.00)	.81

Chi-square test, [a]*t* test, and [d]Fisher's exact test comparing patients with and without EV infections.

[b]Urbanization was categorized into 4 levels depending on the population density of the residential area, with level 1 being the most urbanized and level 4 being the least urbanized.

[c]Other occupations primarily included retired, unemployed and low-income populations.

Table 4 shows that compared with the non-EV cohort, the aHR of asthma increased to 77.9 (95% CI = 75.7-80.1) for patients with EV infection who had more than 5 medical visits per year (*P* for trend <.001). Similar trends were also observed for girls and boys.

4 | DISCUSSION

The most crucial finding of this study is that the risk of incident asthma was higher in the EV cohort than in the non-EV cohort, comprising children aged 0-5 years (<1,[20] 1-3 and 3-5 years[2,21]), regardless of sociodemographic factors[22] (urbanization level[22] and parental occupation[10]), seasonal change[23] and comorbidities. The association of EV infection with asthma is a novel finding, which has rarely been previously reported[24]; thus, EV may play a key role in asthma.[25] Previous studies have found that asthma is associated with EV infection among children aged <1,[6] 1-3 and 3-5 years,[2] consistent with our finding.

EV68 infection has been found to be associated with asthma attacks in children in Japan[21] and the United States.[26] In a study conducted in Taiwan,[27] the incidence of asthma was higher in the EV cohort than in the non-EV cohort (8.72% vs 4.41%, $P < .001$). In the present study, to avoid the effects of confounding factors, we adjusted the HRs for respiratory infections (eg influenza, rhinovirus, mycoplasma, pneumonia and ARIs) and atopic diseases (AR and AD). After the adjustment of the HRs, the aHRs

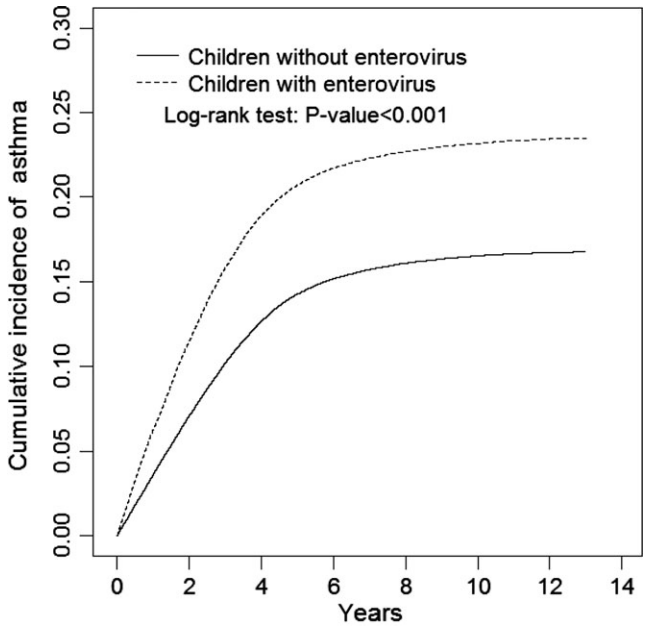

FIGURE 1 Kaplan-Meier analysis of cumulative incidence of asthma for enterovirus (EV) and non-EV cohorts

of asthma remained high in children in the EV cohort with comorbidities (aHR = 1.47) and without comorbidities (aHR = 1.79).

No study has evaluated the relationship of the season and frequency of admission with the incidence of asthma in patients with EV infection. Our study revealed that the risk of incident asthma increased regardless of the season (for each season, $P < .001$). Moreover, the risk of incident asthma was higher in patients with a higher frequency of admission. The damage caused by EV infection was reported to aggravate chronic inflammation in the airway among infants and young children,[28] thus contributing to the development of incident asthma among these patients. Moreover, the seroprevalence of the EV71 IgE Ab is increased in patients with asthma,[7] supporting this finding.

Currently, no preventive vaccines for EV and no highly efficacious medicines to eliminate the virus after it enters the human body are available. Therefore, EV infections will continue to pose a threat to human health in the foreseeable future. Deficits in lung function[29] that are apparent in early adulthood[30] might place patients at risk of subsequent chronic airway diseases[31] such as asthma.[32] In the present study, our observation that the incidence of asthma after follow-up (7.43 years for the EV cohort; 7.95 years for the non-EV cohort) was higher in the EV cohort than in the non-EV cohort agrees with this finding regarding the risk of subsequent chronic airway diseases. Furthermore, this study highlights that EV infections play a role in the potential risk of incident asthma from infancy[33] to 5 years of age. Physicians should be made aware of the possibility of asthma in infants and children with EV infections, thereby facilitating the early detection of incident asthma.

4.1 | Strengths

Currently, EV-coxsackie, ECHO and EV71 viruses are the dominant strains that are spreading globally. To prepare for a potential large-scale EV71 outbreak,[13] the Taiwan Centers for Disease Control (CDC) invited experts and commanders of the Communicable Disease Control Medical Network to formulate response strategies. With the help of the experts, the Taiwan CDC-created clinical guidelines for the management of an EV71 outbreak and made them available to healthcare professionals. Moreover, nearly 76 hospitals were designated as EV treatment centres and were subsidized to implement healthcare quality improvement. The policy for EV infection control is well established in Taiwan (Taiwan CDC website at http://www.cdc.gov.tw or call the toll-free Communicable Disease Reporting hotline). EV diagnosis was validated under the services of the Taiwan CDC. Moreover, the system for the management of asthma[19] is well established[34] in Taiwan. Because of the comprehensive healthcare insurance system, the majority of the population of Taiwan can afford the medical expenses of diseases.[35] These policies avoid diagnosis bias[36] and afford opportunities to follow-up children with asthma.

4.2 | Limitations

This study has several limitations. First, respiratory picornaviruses and respiratory syncytial virus are the causative agents of acute expiratory wheezing in children. Because the causative pathogens of all respiratory tract infections are analysed using throat swabs or NPA, the results might be misinterpreted in the case of concurrent acute infections. Therefore, further surveillance of EV prevalence in healthy controls may be required. Second, asymptomatic EV infections may have been missed in the database. Third, data on cytokine and pulmonary test results are not available in the NHIRD. Fourth, environmental factors such as smoking, food and maternal allergy history (eg asthma), and lifestyle (eg breastfeeding) were not analysed. Finally, a physician-based sentinel surveillance system for infectious diseases was established in Taiwan and is operated by the Ministry of Health. This system includes 850 physicians, representing 8.7% of the primary physicians in Taiwan. The most common clinical manifestations of EV infection, such as HFMD and herpangina, are included in this system[14] (Appendix Table 1). Therefore, even mild cases of EV infection can be detected in Taiwan. The mean number of physicians who reported between 1998 and 2005 was 800, which is 8.5% of all the primary physicians.[15] However,

TABLE 2 Comparison of the risk of asthma between children with and without enterovirus (EV) infections stratified by demographics in Cox proportional hazard regression analysis

	Non-EV			EV			Adjusted HR[a]
	Event	Person-years	IR	Event	Person-years	IR	(95% CI)
All	34 898	1 654 488	21.1	49 044	1 546 186	31.7	1.48 (1.45, 1.50)***
Stratified age							
<1	8531	336 435	25.4	12 769	337 136	37.9	1.49 (1.45, 1.53)***
1-3	21 786	989 601	22.0	29 490	893 685	33.0	1.47 (1.44, 1.50)***
3-5	4581	328 452	14.0	6785	315 365	21.5	1.50 (1.45, 1.56)***
Sex							
Girl	14 441	792 977	18.2	20 722	7 470 944	27.7	1.49 (1.46, 1.53)***
Boy	20 457	861 511	23.8	28 322	799 092	35.4	1.46 (1.43, 1.49)***
Urbanization level[b]							
1 (highest)	10 350	434 372	23.8	13 462	411 589	32.7	1.36 (1.33, 1.39)***
2	11 330	500 323	22.7	15 699	468 136	33.5	1.46 (1.43, 1.50)***
3	6550	340 599	19.2	9419	319 095	29.5	1.50 (1.45, 1.55)***
4 (lowest)	6668	379 193	17.6	10 464	347 367	30.1	1.66 (1.61, 1.71)***
Parental occupation							
White collar	24 925	1 081 827	23.0	33 942	1 019 091	33.3	1.42 (1.40, 1.45)***
Blue collar	6339	353 031	18.0	9490	321 906	29.5	1.60 (1.55, 1.65)***
Others[c]	3634	219 629	16.6	5612	205 189	27.4	1.61 (1.54, 1.68)***
Comorbidity[d]							
No	293	16 585	17.7	583	17 506	33.3	1.79 (1.55, 2.06)***
Yes	34 605	1 637 902	21.1	48 461	1 528 680	31.7	1.47 (1.45, 1.49)***

IR, incidence rate, per 1000 person-years.

[a]Adjusted HR, adjusted for age, sex, urbanization level, parental occupation and comorbidities of allergic rhinitis, atopic dermatitis, acute respiratory infections, pneumonia and influenza, other diseases of the upper respiratory tract, rhinovirus infection and mycoplasma.

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

[c]Other occupations primarily included retired, unemployed and low-income populations.

[d]Comorbidity: Patients with any one of the comorbidities of allergic rhinitis, atopic dermatitis, acute respiratory infections, pneumonia and influenza, other diseases of the upper respiratory tract, rhinovirus infection and mycoplasma were classified as the comorbidity group.

***$P < .001$.

TABLE 3 Incidence rate and hazard ratios of patients with asthma stratified by season of enterovirus (EV) infections estimated using Cox proportional hazard regression analysis

Variable (ICD-9-CM)	No.	Event	Person-years	IR	Adjusted HR[a] (95% CI)
Non-EV cohort	208 213	34 898	1 654 488	21.1	1 (Reference)
Season of EV					
1-3 mo	21 476	5335	165 579	32.2	1.54 (1.50, 1.59)***
4-6 mo	88 668	20 359	685 056	29.7	1.43 (1.41, 1.46)***
7-9 mo	56 438	13 502	401 580	33.6	1.51 (1.48, 1.54)***
10-12 mo	41 631	9848	293 971	33.5	1.49 (1.46, 1.52)***

IR, incidence rate, per 1000 person-years.

[a]Adjusted HR, adjusted for age, sex, urbanization level, parental occupation and comorbidities such as allergic rhinitis, atopic dermatitis, acute respiratory infections, pneumonia and influenza, other diseases of the upper respiratory tract, rhinovirus infection and mycoplasma.

*$P < .05$, **$P < .01$, ***$P < .001$.

TABLE 4 Risk of asthma among patients with asthma stratified by average frequency of medical visits for enterovirus (EV) infections in Cox proportional hazard regression

Average frequency for medical visit, per years	Event	Person-years	IR	Adjusted HR[a] (95% CI)
All				
None	34 898	1 654 488	21.1	1.00 (Reference)
≤3	35 924	1 535 087	23.4	1.10 (1.08, 1.11)***
4-5	5983	8000	747.9	21.6 (21.0, 22.2)***
>5	7137	3099	2302.7	77.9 (75.7, 80.1)***
P for trend				<.001
Girl				
None	14 441	792 977	18.2	1.00 (Reference)
≤3	15 299	742 343	20.6	1.12 (1.09, 1.14)***
4-5	2474	3418	723.8	25.1 (24.0, 26.2)***
>5	2949	1332	2213.4	86.4 (82.6, 90.3)***
P for trend				<.001
Boy				
None	20 457	861 511	23.8	1.00 (Reference)
≤3	20 625	792 744	26.0	1.08 (1.06, 1.10)***
4-5	3509	4582	766.0	19.5 (18.8, 20.3)***
>5	4188	1767	2370.0	72.3 (69.6, 75.1)***
P for trend				<.001

IR, incidence rate, per 1000 person-years.

[a]Adjusted HR, adjusted for age, sex, urbanization level, parental occupation and comorbidities such as allergic rhinitis, atopic dermatitis, acute respiratory infections, pneumonia and influenza, other diseases of the upper respiratory tract, rhinovirus infection and mycoplasma.

*$P < .05$, **$P < .01$,***$P < .001$.

EV infection in young children without significant clinical symptoms or signs may have been undetected, contributing to underdiagnosis. This is may be another limitation of this study.

5 | CONCLUSION

The incidence of asthma was higher in the EV cohort than in the non-EV cohort, comprising children ≤5 years, regardless of sex, urbanization level, parental occupation or season. In particular, the risk of asthma was higher in children with a higher frequency of admission, even in the absence of atopy or other respiratory infections.

AUTHOR CONTRIBUTIONS

Wu-Huei Hsu and Jun-Jun Yeh involved in supervision and project administration. Wu-Huei Hsu carried out funding acquisition. All authors involved in conceptualization, methodology, formal analysis, investigation and writing (original draft preparation) of the data.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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APPENDIX

TABLE A1 Children aged 0 ~ 18 years (including aged <5 years). Incidence rate and hazard ratio of asthma in patients by type of enterovirus infection (EV infection) estimated using Cox proportional hazard regression analysis

Variable (ICD-9-CM)	No.	Event	Person-years	IR	Adjusted HR[a] (95% CI)
Non-EV infection cohort	230 669	36 805	1 829 383	20.1	1 (Reference)
Subtype of EV infection					
Enteritis due to enterovirus (008.67)	18	5	94	53.3	2.06 (0.86, 4.94)
Meningitis due to enterovirus (047)	422	78	3318	23.5	1.39 (1.11, 1.73)**
Other enterovirus diseases of central nervous system (048)	159	36	1180	30.5	1.59 (1.15, 2.21)**
Specific diseases due to coxsackievirus (074)	229 857	51 941	1 710 723	30.4	1.47 (1.45, 1.49)***
Herpangina (074.0)	185 872	42 858	1 364 003	31.4	1.49 (1.47, 1.51)***
Epidemic pleurodynia (074.1)	26	9	176	51.1	2.32 (1.21, 4.46)*
Coxsackievirus carditis (074.2)	21	6	164	36.7	1.66 (0.75, 3.69)
Hand-foot-and-mouth disease (074.3)	41 599	8529	325 466	26.2	1.41 (1.37, 1.44)***
Other specified diseases due to coxsackievirus (074.8)	2339	539	20 913	25.8	1.33 (1.22, 1.44)***
Echovirus infection in conditions classified elsewhere and of unspecified site (079.1)	45	17	275	61.8	3.06 (1.91, 4.92)***
Coxsackievirus infection in conditions classified elsewhere and of unspecified site (079.2)	168	35	1295	27.0	1.46 (1.05, 2.03)*

IR, incidence rate, per 1000 person-years.

[a]Adjusted HR, adjusted for age, sex, urbanization level, parental occupation and comorbidity of allergic rhinitis, atopic dermatitis, acute respiratory infections, pneumonia and influenza, other diseases of upper respiratory tract, rhinovirus infection and mycoplasma.

*$P < .05$, **$P < .01$; ***$P < .001$.