

Association between depression and enterovirus infection

A nationwide population-based cohort study

Yin-To Liao, MD^{a,b}, Ming-Hong Hsieh, MD, PhD^{a,b}, Yao-Hsu Yang, MD^{c,d}, Ying-Ching Wang, medical student^e, Ching-Shu Tsai, MD^{f,g}, Vincent Chin-Hung Chen, MD, PhD^{f,g,*}, Michael Gossop, MD, PhD^h

Abstract

Enterovirus (EV) infection is common among children and adolescents. Few studies have investigated the relationship of depression after EV infection. This study explores an association between EV infection and subsequent depression in children and adolescents and assesses the risk of depression after EV infection with central nervous system involvement in a nationwide population-based retrospective cohort.

A random sample of 1,000,000 people was derived from Taiwan National Health Insurance Research Database and we identified enrollees less than 18 years with EV infection before 2005 and followed up until December 2009. A total 48,010 cases with EV infection and 48,010 healthy controls matched for sex, age, and residence were obtained. Association between EV infection and depression risk was assessed by Cox proportional hazards models to determine the hazard ratios (HRs) and confidence intervals (CIs). We further stratified EV infection into with central nervous system (CNS) involvement and without and compared with matched cohort.

Children and adolescents with EV infection had no elevated risk of depression compared with healthy controls (adjusted HR, aHR = 1.00, 95% CI: 0.83–1.21). However, CNS EV infection was associated with increased risk of depression (aHR = 1.62, 95% CI: 1.02–2.58) in the fully adjusted Cox regression model.

To the best of our knowledge, this is the first study investigating depression in children and adolescents with CNS EV infection. The results suggested that children and adolescents with CNS EV infection were a susceptible group for subsequent depressive disorders.

Abbreviations: CI = confidence intervals, CNS = central nervous system, EV = enterovirus, HFMD = hand-foot-and-mouth disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Clinical Modification, IFN- γ = interferon gamma, IL = interleukin, ME = meningoencephalitis, NHI = National Health Insurance, TNF- α = tumor necrosis factor alpha.

Keywords: central nervous system, depression, enterovirus

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M-HH contributed equally as the first author.

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^a Department of Psychiatry, Chung Shan Medical University Hospital,

^b Department of Psychiatry, School of Medicine, Chung Shan Medical University,

^c Institute of Occupational Medicine and Industrial Hygiene, National Taiwan

University, Taipei, ^d Department of Traditional Chinese Medicine, Chang Gung

Memorial Hospital, Puzi City, Chiayi, ^e School of Medicine, Fu Jen Catholic

University, Taipei, ^f Chang Gung Medical Foundation, Chiayi Chang Gung

Memorial Hospital Chiayi, ^g Chang Gung University, Taoyuan, Taiwan, ^h National

Addiction Centre, King's College, London, UK.

* Correspondence: Vincent Chin-Hung Chen, Chang Gung Medical Foundation, Chiayi Chang Gung Memorial Hospital, No.6, W. Sec., Jiapu Rd., Puzi City, Chiayi County, 613, Taiwan (e-mail: hjcch@yahoo.com.tw).

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1. Introduction

Epidemiological studies have shown that major depression is comparatively rare among children, but more common among adolescents, with up to an 11% lifetime prevalence by the end of adolescence.^[1] About 3% of prepubertal children and 6% of postpubertal children and adolescents were noted to suffer from depressive disorders.^[2] Depressive disorder beginning early in life can lead to impairment in physical activities and has serious functional consequences.^[3] Understanding the depressive disorder during this developmental stage may be critical for developing effective intervention strategies. Most children with depression will suffer from some noticeable changes in social and physical activities, a loss of interest in attending school, or poor academic performance.^[4] Children may also have illegal substance abuse, alcohol use, or cigarettes smoking related to depressed mood, and these maladaptive behaviors further exacerbate depression.^[5] The causes of depression in children and adolescents remain largely unknown. Depression may be due to any combination of poor physical health, environment stress, genetic vulnerability, and life events such as being abused, losing a parent or divorce of parents.^[6] Early onset of major depression is an established risk factor for depression in adulthood.^[7,8]

Major depressive disorder is associated with increased production of proinflammatory cytokines, such as interleukin-1

(IL-1), IL-6, and interferon gamma (IFN- γ).^[9] Some chronic viral infections are also known to increase inflammatory cytokine like IL-1, IL-6, and tumor necrosis factor alpha (TNF- α).^[10,11] The inflammatory model of depression provides a possible link between the infection and major depressive disorder. Research has shown that some mental disorders are related to chronic viral infection.^[12–14] Increased macrophage migration inhibitory factor was found in patients with major depression.^[15] Serum high-sensitivity C-reactive protein was an independent risk factor for major depressive disorder in women in 1 retrospective cohort study. Results supported an etiological role for inflammatory activity in the pathophysiology of depression.^[16] One population-based study indicated that influenza infection was a risk factor for subsequent depressive disorders.^[17] Dysfunction of the immune and inflammatory system has been found in a subgroup of treatment-resistant affective and schizophrenic spectrum disorder patients.^[18] Noncentral nervous system (CNS) pathogenic microorganisms (i.e., in the gastrointestinal tract) may also activate the immune system and produce serotonin and gamma-aminobutyric acid, which act on the gut–brain axis and exert its effect on depression.^[19]

The genus Enterovirus belongs to one of the families of Picornaviridae, and it is composed of icosahedral, nonenveloped, and single-stranded RNA viruses.^[20] Enterovirus consists of several species that are defined by the molecular structure and serological characteristics. Enterovirus contains the following species: Enterovirus (EV)-A that includes EV-71 and some Coxsackievirus group A viruses, EV-B that includes Coxsackievirus group B viruses and echoviruses, EV-C that includes polioviruses 1 to 3, EV-D that includes EV-68 and 70, and the rhinoviruses.^[21] EV are known to cause a spectrum of clinical manifestations in humans. Most EV infections are asymptomatic or mild, such as upper respiratory infection, herpangina, and hand-foot-and-mouth disease (HFMD). The more severe syndromes associated with EV were meningitis, encephalitis, myocarditis, and sepsis. Since its discovery in 1969, EV-71 has been identified as the cause of epidemic HFMD associated with severe neurological complications, including aseptic meningitis, brainstem encephalitis, acute flaccid paralysis, and neurogenic pulmonary edema in children under 5 years of age.^[22] Human EV-71 has emerged as an important etiology of viral encephalitis throughout the Asia-Pacific region over the past 15 years. Increased epidemic activity and endemic circulation of EV-71 has also been observed since 1997, and this may be associated with the regular emergence of new genetic lineages.^[23] During the EV-71 outbreak in Taiwan in 1998, there were more than 130,000 cases of HFMD with 405 severe cases and 78 deaths.^[24] Despite that most of the HFMDs caused by EV-71 will not induce serious complications, high rates of neurological complications, such as meningoencephalitis (ME), pulmonary complications, and even fatal cases, were noted during the outbreaks of HFMD caused by EV-71 from 2000 to 2002.^[25] Most survivors of brainstem encephalitis with cardiopulmonary failure have long-term neurologic sequelae, psychiatric disorders, and impaired cognition in young children.^[26,27] Although EV infection is common among children and adolescents, very few studies have investigated the relationship of psychiatric sequelae after EV infection. We hypothesized that EV infection is related to depression in children and adolescents and that the severe form of EV infection further elevates the risk. We tested the hypothesis in the nationwide population-based retrospective cohort.

2. Materials and methods

2.1. Database

The data were derived from the Taiwan National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) established a single-payer insurance system in Taiwan since 1995. The disbursement of all national healthcare funds covering ambulatory, outpatient, dental services, and hospital inpatient care was centralized by this government insurer. The characteristics of NHI include 1 global budget, payroll-based premiums shared by employers, employees and the government, and the case payment system. Since NHI launched in 1995, the coverage rate rose from 92% in the beginning to 99.5% of medical claims in 2009 in Taiwan. The registration of all medical claims is demanded by the bureau of NHI. The data of registration include demographic data of patients, dates and numbers of clinical visits, medical prescriptions, physician specialties, and diagnostic codes of the Ninth Revision of the International Classification of Diseases, Clinical Modification (ICD-9-CM). The NHIRD gathers these data and provides a random sample of 1,000,000 people (about 5% of the national population of Taiwan) from the registry of NHI enrollees for research use. A systemic sampling method is applied and there is no statistically significant difference in age, sex, or health care utilization between the sample and total enrollees.^[28]

2.2. Study subjects and design

This study used a population-based retrospective cohort from the Longitudinal Health Insurance Database. The cohort was composed of insured children under 18 years old before 2005 with EV infection and followed up until December 2009. We identified 48,340 children with incident diagnose of EV infection within the observation period. The EV infection was defined as having at least 2 outpatient diagnoses within 1 year or at least 1 inpatient diagnosis of EV infection. The diagnostic codes of EV infection included meningitis due to EV (ICD-9-CM codes 047, 047.0, and 047.1), other EV diseases of CNS (ICD-9-CM codes 048), specific diseases related to Coxsackievirus (ICD-9-CM codes 074, 074.0, 074.1, 074.2, 074.20, 074.21, 074.23, 074.3, and 074.8), Echovirus and Coxsackievirus infection in conditions classified elsewhere and of unspecified site (ICD-9-CM codes 079.1 and 079.2), and enteritis due to EV (ICD-9-CM codes 008.67).^[29] Exclusion criteria were age 18 years old or older and diagnosis of depression before EV infection. We matched the study cohort with 1 control per case from the remaining sample without EV infection by randomly sampling and matching for sex, age, residence, and the index date of EV infection diagnosed. The process of obtaining the analyzed sample is shown in Fig. 1. EV with CNS involvement was defined by the diagnosis of encephalitis in viral diseases (ICD-9-CM codes 323.0), other encephalitis due to infection (ICD-9-CM codes 323.4), and unspecified cause of encephalitis (ICD-9-CM codes 323.9), which were diagnosed within 1 month after diagnosis of EV infection.

2.3. Case identification of depression

Cases with the diagnosis of major depressive disorder, single episode (ICD-9-CM code 2962), major depressive disorder, recurrent episode (ICD-9-CM code 2963), neurotic depression (ICD-9-CM code 3004), or depressive disorder, not elsewhere classified (ICD-9-CM code 311) were identified as depression in this study. Those who had at least 2 outpatient diagnoses within 1

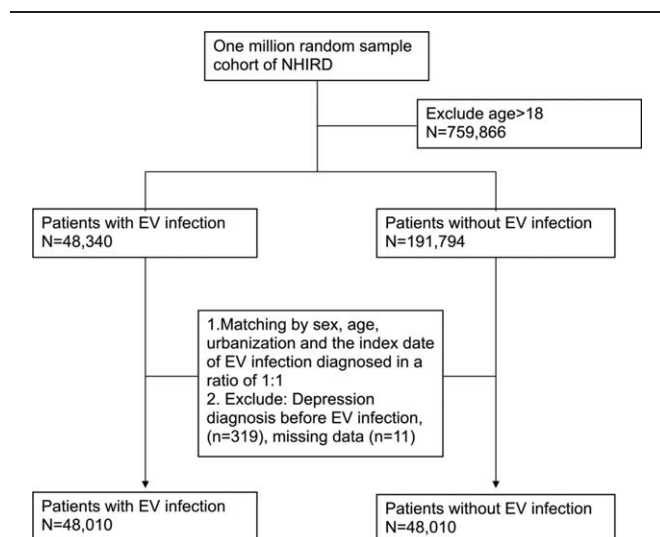


Figure 1. Flow chart of data collection for ICD codes of EV infection and matching cohort. EV = enterovirus, ICD = International classification of diseases.

year or at least 1 inpatient diagnosis were included in the study analysis. The definition is the same as previous studies.^[30]

2.4. Confounding factors

The pathogenesis of depression remains unclear.^[31] Several risk factors for depression including genetic inheritance, low birth weight, psychosocial stress, allergic disease, and traumatic brain injury have been reported.^[32,33] In this study, low birth weight (ICD-9-CM codes 760–764, 766–779, and V137) and allergic diseases, such as asthma (ICD-9-CM code 493), allergic rhinitis (ICD-9-CM code 477.9), allergic conjunctivitis (ICD-9-CM codes 372.05, 372.14), and atopic dermatitis (ICD-9-CM codes 691, 691.8) were identified as risk factors for depression and adjusted in Cox regression analysis. The ICD codes used in the study are shown in supplement Table 1, <http://links.lww.com/MD/B546>.

2.5. Ethics

No identifying information from any of the subjects was available or accessed. Institutional Review Board approval was approved at Chang Gung Medical University Hospital.

2.6. Statistical analysis

Descriptive analyses were carried out for the distribution of demographic factors and the frequency of comorbidities in the groups of the children with and without EV infection. The log-rank test was used to investigate variation in the chance for depression and Cox proportional hazards models were applied to determine the hazard ratios (HRs) accompanying 95% CIs after adjusting for sex, age at entry, residence, asthma, allergic rhinitis, atopic dermatitis, conjunctivitis (including acute atopic conjunctivitis, and other chronic allergic conjunctivitis), disorders related to short gestation and unspecified low birth weight, and years of follow-up. Significant differences were defined as 2-tailed P value ≤ 0.05 . The death date was retrieved from the national mortality database. Enrollees with a death date or loss of follow-up during the study period were excluded from analyses. All analyses in our study were performed using SAS statistical software (Version 9.4; SAS Institute, Cary, NC).

Table 1

Characteristics of EV infection cases and their matched controls.

Characteristic	EV infection		Non-EV infection		χ^2 test P value
	N	%	N	%	
Sex					
Girl	22,252	46.35	22,252	46.35	1.000
Boy	25,758	53.65	25,758	53.65	
Age at entry, y					
≤ 1	4026	8.39	4026	8.39	1.000
$>1-3$	8964	18.67	8964	18.67	
$>3-5$	9216	19.20	9216	19.20	
$>5-10$	20,925	43.58	20,925	43.58	
>10	4879	10.16	4879	10.16	
Residence					
1 (City)	13,328	27.76	13,328	27.76	1.000
2	23,058	48.03	23,058	48.03	
3	8075	16.82	8075	16.82	
4 (Village)	3549	7.39	3549	7.39	
Allergic rhinitis					
No	20,499	42.70	26,048	54.26	$<0.001^\dagger$
Yes	27,511	57.30	21,962	45.74	
Atopic dermatitis and related conditions					
No	37,286	77.66	39,834	82.97	$<0.001^\dagger$
Yes	10,724	22.34	8176	17.03	
Conjunctivitis*					
No	32,667	68.04	35,201	73.32	$<0.001^\dagger$
Yes	15,343	31.96	12,809	26.68	
Disorders relating to short gestation and unspecified low birthweight					
No	43,508	90.62	43,885	91.41	$<0.001^\dagger$
Yes	4502	9.38	4125	8.59	
Asthma					
No	31,346	65.29	35,915	74.81	$<0.001^\dagger$
Yes	16,664	34.71	12,095	25.19	
Depression					
No	47,784	99.53	47,804	99.57	0.360
Yes	226	0.47	206	0.43	
Follow year	9.72 \pm 3.59		9.72 \pm 3.59		0.964

EV = enterovirus.

* Conjunctivitis includes acute atopic conjunctivitis and other chronic allergic conjunctivitis.

$^\dagger P < 0.05$.

3. Results

3.1. Characteristics of the subjects

Two study groups were patients with EV infection (N=48,010) and without EV infection (N=48,010). EV infection with CNS involvement was identified in 1192 patients (supplement Table 2, <http://links.lww.com/MD/B546>). The characteristics of cases with EV infection and the matched controls are shown in Table 1. There were significant differences between 2 groups in allergic rhinitis ($P < 0.001$), atopic dermatitis and related conditions ($P < 0.001$), conjunctivitis (P value < 0.001), asthma ($P < 0.001$), and disorders related to short gestation and unspecified low birth weight ($P < 0.001$). A total of 432 patients received the diagnosis of depression during the study period: 226 (0.47%) in EV infection cohort and 206 (0.43%) cases in non-EV infection cohort.

3.2. Association between EV infection and risk of depression

Analysis of the association between EV infection and risk of depression is shown in Tables 2 and 3. There was no difference in risk for depression between the EV infection and non-EV infection cohorts after adjusting for sex, age, residence, atopic

Table 2**Cox proportional hazard regression analysis for the adjusted HRs of depression for enterovirus infection, demographic characteristics, and comorbidity.**

Variables	Unadjusted hazard ratio			Adjusted hazard ratio		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
EV infection						
No (reference)	1.000			1.000		
Yes	1.097	0.909–1.325	0.335	0.999	0.826–1.209	0.994
Sex						
Girl (reference)	1.000			1.000		
Boy	0.809	0.670–0.977	0.028 [†]	0.772	0.639–0.933	0.007 [†]
Age at entry, y						
≤1 (reference)	1.000			1.000		
>1–3	0.711	0.223–2.273	0.566	0.705	0.221–2.254	0.556
>3–5	0.811	0.274–2.399	0.705	0.801	0.270–2.371	0.688
>5–10	2.132	0.783–5.802	0.139	2.174	0.797–5.927	0.129
>10	6.471	2.369–17.679	<0.001 [†]	7.286	2.660–19.958	<0.001 [†]
Residence						
1 (City)	1.644	1.066–2.534	0.024 [†]	1.342	0.869–2.072	0.185
2	1.357	0.889–2.070	0.157	1.201	0.787–1.834	0.395
3	1.025	0.637–1.649	0.920	0.954	0.593–1.536	0.846
4 (Village, reference)	1.000			1.000		
Allergic rhinitis						
No (reference)	1.000			1.000		
Yes	1.684	1.383–2.050	<0.001 [†]	1.552	1.253–1.922	<0.001 [†]
Atopic dermatitis and related conditions						
No (reference)	1.000			1.000		
Yes	1.253	0.986–1.593	0.065	1.404	1.094–1.801	0.008 [†]
Conjunctivitis*						
No (reference)	1.000			1.000		
Yes	1.206	0.986–1.474	0.068	1.088	0.885–1.337	0.424
Disorders relating to short gestation and unspecified low birthweight						
No (reference)	1.000			1.000		
Yes	0.951	0.676–1.337	0.771	1.323	0.930–1.882	0.120
Asthma						
No (reference)	1.000			1.000		
Yes	1.337	1.097–1.629	0.004 [†]	1.237	0.997–1.533	0.053

EV = enterovirus, HR = hazard ratio.

* Conjunctivitis includes acute atopic conjunctivitis and other chronic allergic conjunctivitis.

[†] $P < 0.05$.

diseases, and disorders relating to short gestation and unspecified low birthweight (adjusted HR, aHR = 0.999, 95% CI: 0.826–1.209).

EV infection was positively correlated with depression in CNS involved cases (aHR = 1.621, 95% CI: 1.018–2.582) in the fully adjusted Cox regression model for HRs after adjusting for sex, age, urbanization, allergic rhinitis, atopic dermatitis and related conditions, conjunctivitis, disorders relating to short gestation and unspecified low birth weight, and asthma. The incidences of depression were consistently higher for the EV infection than non-EV infection cohort with entry age more than 10 years old (adjusted HR = 7.080, 95% CI: 2.583–19.402), allergic rhinitis (aHR = 1.546, 95% CI: 1.248–1.915), atopic dermatitis and related conditions (aHR = 1.402, 95% CI: 1.093–1.798), and lower incidence of depression with boy (aHR = 0.768, 95% CI: 0.636–0.928).

4. Discussion

To the best of our knowledge, the present study is the first nationwide population-based cohort study to investigate the relationship between EV infection and depression in children under 18 years old. The results indicated that CNS EV infection

increased by more than 60% the HR of depression compared with healthy control after adjusting for sex, age, residence, short gestational age, unspecified low birth weight, asthma, and atopic diseases, whereas EV infection per se did not increase the risk of subsequent depression.

Depression is a heterogeneous psychological disorder with multiple biological and psychosocial risk factors. Viral infection has been postulated as one of the risk factors of depression, and human immunodeficiency virus, hepatitis C virus, varicella-zoster virus, and human T-cell lymphotropic virus have been found to be related to depression.^[34–37] There is only 1 small case series study (n = 39) in 1989 which considers the role of EV in depressive-like symptoms. Wilson et al^[38] found that a combination of dysphoric symptoms, such as unexplained crying with clinging, anxious behavior, and preoccupation with death, was observed in children with Coxsackievirus B infection. The present study investigated depression related to more species of EV than the previous studies and in a much larger population. The results were in line with previous studies that CNS EV infection was positively associated with depression. Furthermore, we added more evidence of the role of EV infection in the development of subsequent depression with a longitudinal design and possible linkage of viral meningoencephalitis and depression.

Table 3**Cox proportional hazard regression analysis for the adjusted HRs of depression for CNS enterovirus infection, demographic characteristics, and comorbidity.**

Variables	Unadjusted hazard ratio			Adjusted hazard ratio		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
EV infection						
No (reference)	1.000			1.000		
EV and non-CNS	1.038	0.856–1.259	0.704	0.964	0.793–1.172	0.712
EV and CNS	2.657	1.676–4.211	<0.001 [†]	1.621	1.018–2.582	0.042 [†]
Sex						
Girl (reference)	1.000			1.000		
Boy	0.809	0.670–0.977	0.028 [†]	0.768	0.636–0.928	0.006 [†]
Age at entry, y						
≤ 1 (reference)	1.000			1.000		
>1–3	0.711	0.223–2.273	0.566	0.706	0.221–2.257	0.557
>3–5	0.811	0.274–2.399	0.705	0.800	0.270–2.371	0.688
>5–10	2.132	0.783–5.802	0.139	2.165	0.794–5.904	0.131
>10	6.471	2.369–17.679	<0.001 [†]	7.080	2.583–19.402	<0.001 [†]
Residence						
1 (City)	1.644	1.066–2.534	0.024 [†]	1.347	0.872–2.079	0.180
2	1.357	0.889–2.070	0.157	1.206	0.790–1.841	0.386
3	1.025	0.637–1.649	0.920	0.958	0.595–1.542	0.860
4 (Village, reference)	1.000			1.000		
Allergic rhinitis						
No (reference)	1.000			1.000		
Yes	1.684	1.383–2.050	<0.001 [†]	1.546	1.248–1.915	<0.001 [†]
Atopic dermatitis and related conditions						
No (reference)	1.000			1.000		
Yes	1.253	0.986–1.593	0.065	1.402	1.093–1.798	0.008 [†]
Conjunctivitis*						
No (reference)	1.000			1.000		
Yes	1.206	0.986–1.474	0.068	1.092	0.888–1.341	0.405
Disorders relating to short gestation and unspecified low birthweight						
No (reference)	1.000			1.000		
Yes	0.951	0.676–1.337	0.771	1.315	0.924–1.872	0.128
Asthma						
No (reference)	1.000			1.000		
Yes	1.337	1.097–1.629	0.004 [†]	1.235	0.996–1.531	0.055

CI = confidence intervals, CNS = central nervous system, HR = hazard ratio.

* Conjunctivitis includes acute atopic conjunctivitis and other chronic allergic conjunctivitis.

[†] P < 0.05.

The pathogenesis of depression has been hypothesized to be related to decreased monoamine neurotransmitter availability. Recently, the implication of immune system in depression has been extensively studied, and this inspired the cytokine hypothesis of depression. Cytokines related to depression included IL-6, IL-1 β , TNF- α , and IFN- γ . The regulation of serotonin transporter function by pro-inflammatory cytokines provides a mechanistic link between the monoamine and cytokine theories of depression.^[39]

A study of cytokine changes in the blood and cerebrospinal fluid (CSF) from 93 children infected with EV-71 showed elevated plasma levels of IL-1 β and IL-6 in cases with CNS involvement when compared with patients with no CNS involvement and normal controls. Higher CSF levels of IL-6, IL-8, and IL-1 β were also found in acute phase in critical patients with CNS involvement.^[40]

A similar study of 97 children with EV-71-related ME found higher levels of IFN- γ and IL-6 in ME than in febrile convulsion. The results might imply the severity CNS involvement correlated with more IL-6 overproduction in CNS inflammatory responses.^[41] Another cross-sectional study enrolled 165 patients with CNS infection and found robust proinflammatory cytokine

pattern, higher levels of IL-6, TNF, and IL-17, in CSF among 13 EV meningoencephalitis cases.^[42] In conclusion, IL-1 β , IL-6, and IFN- γ were associated with EV-71-induced neuropathology and depression might serve as a part of the neurological sequelae of CNS EV infection. This might provide an explanation for the differences between CNS and non-CNS EV infection on subsequent depression risks.

Atopy diseases, except asthma, were positively associated with depression risks in our results. Previous studies presented mixed results whether persons with asthma had elevated risk for depression.^[43]

The present study is the first to utilize a comprehensive and large representative nationwide population-based cohort to investigate the association between EV infection and subsequent depression. The longitudinal analysis from the registration medical claim based data avoided recall bias. The use of a population-based cohort prevented selection bias. By excluding depression before EV-related diagnoses, we eliminated the reverse causal relationship between EV infection and depression. Nevertheless, there were several limitations of our study. First, we defined depression with a more broad range of diagnoses, including major depressive disorder, single and recurrent episode,

neurotic depression and depressive disorder, not elsewhere classified (NOS). Neurotic depression and depression NOS comprised a heterogeneous patient group with overlapping minor mental disorders such as anxiety and adjustment disorder. There is also a strong association between hospitalization, depressive, and anxiety disorders.^[44] Thus, depression could be the result of hospitalization, burden from severe physical illness, or disability that was not the direct effect of EV infection per se. In a subgroup analysis, we found patients with EV infection-related hospitalization had a nonsignificant risk for depression (HR 1.315, 95% CI: 0.997–1.735, not shown in table) compared with patients with nonhospitalized EV infection and healthy controls in the adjusted model. The Taiwan NHIRD lacked the data of extent of disability and disease burden and thus no further stratification of patient groups or analysis was performed. We matched the study cohort in large sample size with the control group for sex, age, and urbanization level of residence to avoid confounding. However, the family psychiatric history, parents' marital status, child abuse, socioeconomic status, and other risk factors for depressive disorders were not included in NHIRD and potential bias was possible. Second, the diagnosis of depression was strictly based on ICD codes rather than a formal diagnostic process such as uniform structured clinical interview or questionnaires. There was no validation study specifically on diagnoses of depression in Taiwan. Central nervous system involvement of EV infection did not require cerebrospinal fluid study as a must to confirm the diagnosis in registration. NHIRD provided no concomitant data to check whether these diagnostic procedures had been performed, either. However, diagnoses in registration data were made by board-certified psychiatrist or physicians and the accuracy of disease diagnoses in national health insurance system had been reported between 60% and 90%.^[45]

We found CNS EV infection was associated with increased risk of depression in children and adolescents in a nationwide population-based cohort study. Future biological research may provide the mechanism or pathophysiology of depression associated with EV infection. In clinical practice, we suggest that children with CNS EV infection should receive proper psychological assessment and monitoring for emerging depression with the rationale of these children being a susceptible group for depressive disorder.

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