Increased Incidence of Pediatric Type 1 Diabetes With Novel Association With Coxsackievirus A Species in Young Children but Declined Incidence in Adolescents in Taiwan

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OBJECTIVE

Type 1 diabetes (T1D) has been linked to enterovirus infection in small population-based epidemiological studies. We investigated the secular relationship of T1D incidence with enterovirus infection and enterovirus species using nationwide population-based analysis.

RESEARCH DESIGN AND METHODS

We accessed the National Health Insurance Research Database of Taiwan to identify T1D and enterovirus infection cases from 2001 to 2015. Enterovirus serotype isolation rates were obtained from the nationwide laboratory surveillance systems. Negative binomial regression models assessed the incidence trend, and extended Cox proportional hazards models analyzed the association of enterovirus infection with T1D incidence. Spearman correlation coefficients evaluated the correlation between T1D incidence and circulating enterovirus species.

RESULTS

T1D incidence rates in youth younger than 20 years were 6.30 and 5.02 per 100,000 person-years in 2001 and 2015 ($P = 0.287$), respectively. T1D incidence increased significantly in children aged 0–6 years ($P < 0.001$) but decreased in adolescents aged 13–19 years ($P = 0.011$). The T1D risk in children aged 0–6 years with enterovirus infection was significantly higher than that in noninfected subjects (hazard ratio 1.46; 95% CI 1.35–1.58; $P < 0.001$). Additionally, TID incidence in children aged 0–6 years was significantly correlated with the isolation rates of coxsackievirus A species ($r = 0.60$; $P = 0.017$), but no association was found beyond the age of 7.

CONCLUSIONS

We demonstrated that T1D incidence increased in children aged 0–6 years but decreased in adolescents aged 13–19 years in Taiwan. Enterovirus-infected subjects younger than 7 years had a higher risk of T1D than noninfected subjects.

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

Type 1 diabetes (T1D) is one of the most important chronic diseases of childhood (1). The incidence of T1D varies widely worldwide. European and North American populations have much higher incidence rates, ranging from 4 to 41 per 100,000 people, than >70% of Asian populations, with incidence rates <1 per 100,000 people (2,3). Regardless of the incidence level, T1D has shown an increasing incidence globally in recent decades (2,4), particularly in the younger population (3,5). Environmental factors have been suggested to play a role in the increasing incidence trend (3,6). The most convincing environmental factor that has been strongly linked to T1D is enterovirus (EV) infection (7).

In Taiwan, the incidence of T1D is relatively low; however, an increasing incidence trend was also observed, particularly in children aged younger than 15 years. The incidence of T1D in male and female individuals aged younger than 15 years has increased from 3.15 and 4.39 per 100,000 individuals during 1992–1996 (8) to 5.88 and 6.92 per 100,000 individuals during 2009–2010 (9). Continuing surveillance to monitor the secular trends and annual change of the T1D incidence for both children and adolescents is warranted to identify youth at increased risks and the public health impact.

The correlation between the secular trend of the T1D incidence and EV infection in Taiwan remains unknown. Recently, a population-based cohort study showed a positive correlation by revealing that EV-infected subjects had a significantly higher incidence of T1D than non–EV-infected subjects, with an incidence rate ratio of 1.48 in Taiwan (10). It remains unclear whether the different types of EV infection have a consistent relationship with T1D.

This study aimed to assess the secular trends of the T1D incidence in youth younger than 20 years and explore the possible correlation of the T1D incidence with EV infection and different types of EV infection in Taiwan, which has a relatively low T1D incidence and high EV infection incidence, by using a nationwide population-based database from 2001 to 2015.

RESEARCH DESIGN AND METHODS

Data Sources and Study Subjects

The National Health Insurance (NHI) program was initiated in Taiwan in 1995 and has provided health care for almost 99% of its citizens (11). The NHI Research Database (NHIRD) was derived from the NHI program and was first maintained by the National Health Research Institutes (NHRI) and then by the Health and Welfare Data Science Center, Ministry of Health and Welfare. The NHIRD systematically collects all the administrative and claims data for research purposes. From NHRI and Health and Welfare Data Science Center, we collected NHIRD data for Ambulatory Care Expenditures by Visits and Registry for Catastrophic Illness Patients from 2001 to 2015 for this study. The definitions of EV infection and T1D were based on the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM).

The study population included nationwide subjects aged younger than 20 years with complete information on sex and age during the study period of 1 January 2001 to 31 December 2015. EV infection was identified using the ICD-9-CM codes 008.67, 047, 047.0, 047.1, 048, 074, 074.0, 074.1, 074.2, 074.20, 074.21, 074.22, 074.23, 074.3, 074.8, 079.1, and 079.2 from the data for Ambulatory Care Expenditures by Visits. Subjects with one ambulatory visit for EV infection during the entire study period were identified as having one infection event. However, one EV infection may contribute to multiple ambulatory visits. Therefore, the interval between ambulatory visits for EV infection of <14 days was identified as one infection event resulting from the same EV infection.

The study outcome was the diagnosis of T1D, identified from the Registry for Catastrophic Illness Patient data (ICD-9-CM codes 250.x1 and 250.x3) during the study period. T1D has been designated a catastrophic illness by the National Health Insurance Administration. All of the applications for catastrophic illness certification are formally and strictly reviewed by National Health Insurance Administration, and the approved patients are eligible for exemption from their copayment for outpatient or inpatient care. Therefore, the diagnosis of T1D showed a high accuracy.

The yearly isolation rates for the top five EV serotypes were obtained from a nationwide laboratory surveillance system of the Taiwan Centers for Disease Control (Taiwan CDC), which was set up to monitor the EV serotypes in communities in 1999. Although the Taiwan CDC only provided the information of yearly isolation rates for the top five EV serotypes, the mean proportion of the yearly sum of the top five EV serotypes proportions from 2001 to 2015 was 77.1%, likely representing the main circulating EV serotypes in communities. This study was approved by the National Taiwan University Hospital Institutional Review Boards (approval number: 201412204RIND).

Statistical Analysis

The incidence rates (per 100,000 person-years) of T1D were calculated by dividing the number of patients diagnosed with T1D (numerator) by the corresponding person-years at risk (denominator). The person-years at risk for study subjects were calculated from their entry into the study (1 January 2001; birth date if born after 1 January 2001) to the diagnosis of T1D, loss to follow-up, death, withdrawal from the NHI program, or the end of the study (31 December 2015).

Negative binomial regression models assessed the secular trends and average annual percent change (AAPC) of the T1D incidence using the observed number of diagnosed T1D cases as the outcome and the natural logarithm of the corresponding denominator (person-years at risk) as the offset. The calendar year was treated as a continuous temporal variable, and AAPC was obtained from the transformation of its coefficient β using the formula $(\exp(\beta)-1)*100$. The unit of observation was the incidence rate in a single calendar year. Negative binomial regression was used because most models in this study showed overdispersion features, which were checked using the deviance divided by its degrees of freedom under the Poisson regression model. Additionally, autocorrelation of the incidence rates was evaluated using the Durbin-Watson statistic. Autoregressive (AR) error

models with first-order autocorrelation [AR(1)] were used for models with serial correlation using the natural logarithm of the incidence rate as the dependent variable and calendar year as the independent variable. The autoregressive error model with AR(1) considers serial correlation by extending the model with an autoregressive model for the random error, which indicates that the error term at time point t is related to that at its previous time point $t-1$. The incidence rates were checked using box-and-whisker plots to identify possible outliers; however, no outlier was observed in our trend analyses.

To examine the relationship between EV infection and the incidence of T1D, extended Cox proportional hazards model analysis with EV infection as a time-dependent covariate and time to T1D onset as the outcome was performed. Hazard ratios (HRs) and the corresponding 95% CIs were calculated by comparing subjects with and without EV infection.

The EVs were classified as EV-A species, EV-B species, coxsackievirus belonging to EV-A species (CVA), and coxsackievirus belonging to EV-B species (CVB) according to the current classification of the International Committee on Taxonomy of Viruses for EV. The EV-A species in this study included CVA2, CVA4, CVA5, CVA6, CVA10, CVA16, and EV-A71. The EV-B species in this study included CVB1, CVB2, CVB3, CVB4, CVB5, CVA9, E6, E11, E18, and E30. The CVA species included CVA2, CVA4, CVA5, CVA6, CVA10, and CVA16, and the CVB species included CVB1, CVB2, CVB3, CVB4, CVB5, and CVA9. The Spearman correlation coefficient (r) was

calculated to evaluate the correlations between the T1D incidence and annual isolation rates of EV species. Subgroup analyses by age and sex were performed. Three age-groups, 0–6, 7–12, and 13–19 years, were used for the analyses (12). Data management and analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC), STATA version 16 (StataCorp, College Station, TX), and Microsoft Excel 2013.

RESULTS

In this study, we identified 4,468 patients with T1D aged younger than 20 years from 2001 to 2015. The mean age of the subjects with T1D onset was 11.3 (SD 4.9) years. The proportions of male and female patients with T1D were 45.9% and 54.1%, respectively.

Age- and Sex-Specific Trends of the T1D Incidence During 2001–2015

The T1D incidence rates of subjects younger than 20 years were 6.30 and 5.02 per 100,000 person-years in 2001 and 2015, respectively, without a significant difference (AAPC = −0.60%; $P = 0.287$) (Table 1). However, the results of the age-specific trend analyses in Table 1 showed a significantly increasing trend in the T1D incidence for children aged 0–6 years (AAPC = 2.68%; $P < 0.001$). By contrast, a significant decreasing trend in the T1D incidence was observed for the population aged 13–19 years (AAPC = −4.22%; $P = 0.011$). Regarding sex, although female subjects had a higher average annual T1D incidence than male subjects (5.83 and 4.56 per 100,000 person-years for female and male subjects, respectively; $P < 0.001$), both groups presented similar decreasing but nonsignificant trend changes

in the T1D incidence (both P for trend >0.05) (Table 1) over the study period.

Figure 1 shows the secular trend of the T1D incidence in different age-groups. The overall trend in youth younger than 20 years decreased without a statistical significance ($P = 0.287$), but the decreasing trend was very significant in adolescents aged 13–19 years ($P = 0.011$). Children younger than 7 years showed an increasing trend ($P < 0.001$), whereas the T1D incidence was stable in children aged 7–12 years ($P = 0.086$).

Association Between the T1D Incidence Risk and EV Infection

We compared the T1D incidence risk between youth with and without EV infection (Fig. 2). In only the children aged 0–6 years, the T1D incidence risk was significantly higher among subjects with EV infection. The HR was 1.46 (95% CI 1.35–1.58; $P < 0.001$) for children aged 0–6, 1.45 (95% CI 1.26–1.67; $P < 0.001$) for boys aged 0–2 years, 1.52 (1.33–1.73; $P < 0.001$) for girls aged 0–2 years, 1.46 (1.15–1.85; $P = 0.002$) for boys aged 3–6 years, and 1.41 (1.14–1.74; $P = 0.002$) for girls aged 3–6 years (Fig. 2). The HR was not significantly higher in children aged 7–19 years with EV infection than in those without.

Correlation of the Taiwan T1D Incidence With Different Species of EV Infection

The correlation of the T1D incidence with the isolation rate of different EV species was further evaluated. Stratified analyses by age-groups indicated that the T1D incidence in children aged 0–6 years was significantly positively correlated with the CVA ($r = 0.60$; $P = 0.017$) isolation rates (Table 2). However, for the children aged 7–12 years and 13–19 years, no significant association was found between the T1D incidence and isolation rates of the different species (Table 2).

CONCLUSIONS

This study revealed that the overall T1D incidence slightly decreased without statistical significance in subjects younger than 20 years. The annual T1D incidence increased significantly in children aged 0–6 years, stabilized in children aged

Table 1—Trend analysis of the T1D incidence during 2001–2015

Characteristics	Subjects (n)	AAPC (%)	95% CI	P values for trend
All subjects†	9,863,412	−0.60	−1.69, 0.50	0.287
Age				
0–6†	5,357,382	2.68	1.23, 4.15	<0.001*
7–12†	1,967,967	0.99	−0.14, 2.12	0.086
13–19‡	2,538,063	−4.22	−6.85, −1.52	0.011*
Sex				
Male‡	5,097,012	−1.21	−3.09, 0.70	0.237
Female†	4,766,400	−0.45	−1.70, 0.81	0.486

*Indicates a statistical significance. †The results of the AAPC and P values for trend were obtained from negative binomial regression model. ‡The results of the AAPC and P values for trend were obtained from autoregressive error model with AR(1).
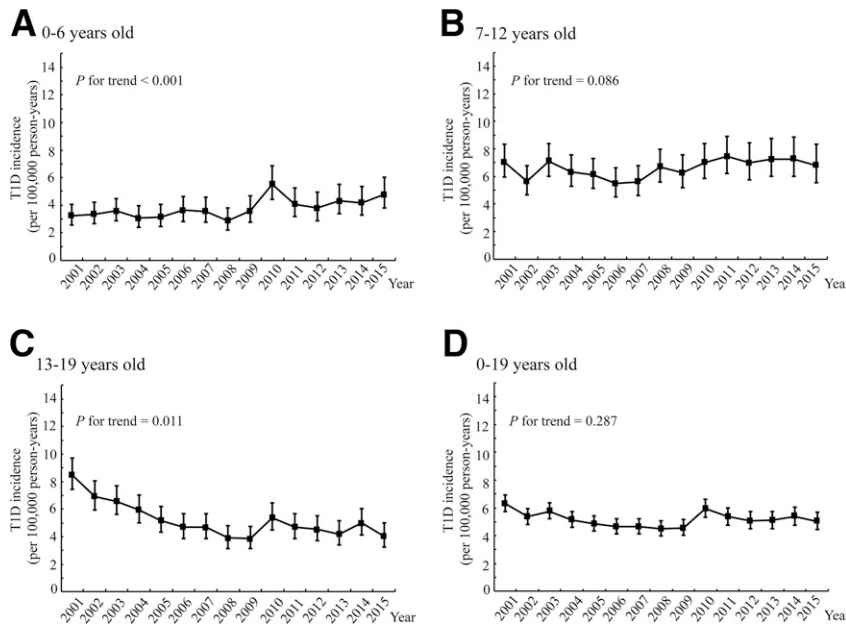
Figure 1—Secular trend of the T1D incidence (per 100,000 person-years) in Taiwan by different age groups during 2001–2015. Subjects aged 0–6 years (A), 7–12 years (B), 13–19 years (C), and 0–19 years (D). The P values for trend were obtained from negative binomial regression models for subjects aged 0–6 years, 7–12 years, and 0–19 years. The P value for trend was obtained from the autoregressive error model with AR(1) for subjects aged 13–19 years. The I bars show the 95% CIs.

7–12 years, and decreased significantly in adolescents aged 13–19 years from 2001 to 2015 in Taiwan. The children aged 0–6 years with EV infection had a significantly higher risk of T1D, with a HR of ~1.46. Moreover, the T1D incidence in children aged 0–6 years was significantly positively correlated with the isolation rates of CVA. The above findings are unique and quite different from those in other reports, particularly from European and North American populations.

Several studies have reported a constant global rise in the incidence of T1D, particularly in young children (5,13). A relatively low rate of increase in incidence was observed in young children in our study, contrasting large studies in Europe and North America where the increase was steeper (5,14). In this study, the AAPC of the T1D incidence in youth aged <20 years was −0.60%, the annual incidence increase in children aged 0–6 years was 2.68%, that in children aged 7–12 years was 0.99%, and that in adolescents aged 13–19 years decreased significantly with an AAPC of −4.22% from 2001 to 2015. Regarding childhood T1D in Europe during 1989–2003, the overall annual increase was 3.9%, and the increases in the 0–4 years, 5–9 years, and 10–14 years age-groups were 5.4%, 4.3%, and 2.9%, respectively (5). In the U.S.,

the overall annual percentage changes in the incidence rates were 1.93% in youth aged <20 years from 2002 to 2015 and 2.44% in adolescents aged 15–19 years (14). The most striking finding in this study was a decrease in the incidence in adolescents, contrasting the trend of the T1D incidence in Western countries (5,14). These findings would add to the further divergence in the incidence rates in Asian subjects versus Caucasoid populations.

The difference in the T1D incidence and its trend in different countries is multifactorial and requires further investigation. Increasing evidence points to major heterogeneity in T1D, even among children, and ethnicity is a major contributor to disease heterogeneity. Our study underscores this notion and clarifies that genetics or race influence the incidence and trend of T1D. Among the genetic factors, DR3 confers the strongest disease risk of T1D. Our previous study revealed that the carrier rate (8.7%) of the most common risk allele, *DRB1*03:01*, in the Taiwanese population is much lower than that (30.3%) of Caucasians, partially explaining the lower incidence of T1D in Taiwan (15,16).

In addition to genetic factors, changes in environmental factors play an important role in the T1D incidence during modernization worldwide. These factors may include life habit changes, such as the overfeeding of children early in life, leading to both accelerated growth and weight, and a moderate excess of child growth that is not necessarily associated with obesity. Accelerated growth and weight may be related to insulin resistance due to excess fat cell accumulation and an increased insulin requirement due to a high growth rate (17). Other factors may include physical stress (infection, inflammation), psychological stress, and the gut microbiota (18). Further investigation is warranted to determine whether significantly different environmental factors contribute to the different trends of the T1D incidence between Western countries and Taiwan.

T1D is a heterogeneous disorder characterized by the destruction of pancreatic β-cells, culminating in absolute insulin deficiency, and most cases are attributed to the autoimmune-mediated destruction of β-cells. A recent study demonstrated that the presence of B lymphocytes and the intracellular distribution of proinsulin
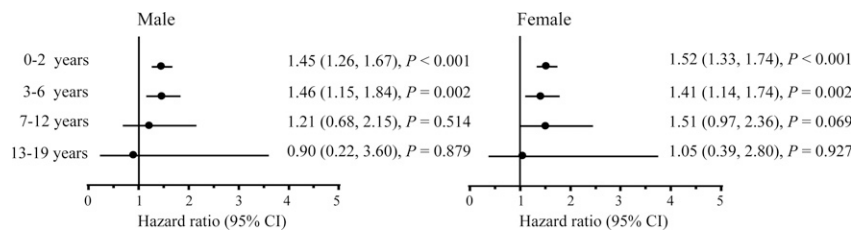

Figure 2—HRs of T1D for male and female subjects according to different age-groups. The HRs were calculated by comparing subjects with and without EV infection. The numbers in parentheses indicate the corresponding 95% CIs of the HRs.

Table 2—Spearman correlation coefficients between the T1D incidence and EV isolation rate during 2001–2015

	EV-A		EV-B		CVA		CVB	
	r	P	r	P	r	P	r	P
T1D								
All (0–19)	0.14	0.629	−0.20	0.481	0.09	0.742	−0.31	0.257
Age 0–6	0.46	0.085	−0.43	0.111	0.60	0.017*	−0.33	0.224
Age 7–12	0.26	0.347	−0.20	0.465	0.22	0.427	−0.04	0.878
Age 13–19	−0.20	0.470	0.16	0.574	−0.21	0.451	−0.12	0.668

P values were obtained from Spearman correlation coefficient (r) analysis. *Indicates a statistical significance.

and insulin in β-cells differed markedly between children developing T1D <7 years and those diagnosed at ≥13 years (12). Our and their studies support that the endotypes of T1D are associated with the diagnosis age. The main paradigm concerning the etiology of T1D hypothesizes that environmentally triggered autoimmune destruction of pancreatic β-cells occurs against the background of genetic risk (19). The search for the triggering factor(s) has been ongoing for the past century, with controversial findings. An important environmental/triggering factor is viral infection, particularly EV infection. The current study investigated the association of the T1D incidence among youth with EV infection by using a nationwide population-based analysis. The T1D incidence risk was significantly higher in children aged 0–6 years with EV infections. With its large sample size and long study duration, our study provided reliable information on the association.

The explanation for the decreasing trend of the T1D incidence in Taiwanese adolescents aged 13–19 years requires further investigation. Because EV infection is one of the most important environmental factors, we speculate that better EV infection control may partly explain the decreasing trend. In 1998, Taiwan experienced the worst EV-A71 epidemic, which resulted in 405 severe cases and 78 deaths (20). After the epidemic, multiple real-time national EV surveillance systems were established by the Taiwan CDC, including a viral laboratory network, outpatient, inpatient, and emergency department visits for hand-foot-and-mouth disease and/or herpangina, and mandatory notification of severe EV cases (21). Real-time EV surveillance makes early detection of EV circulation possible,

and strict implementation of preventive measures during the circulation periods is applied, limiting the spread of the EV (22). For example, to reduce the risk of EV clustering, class suspension is executed for preschool education and day care institutions. Strengthened implementation of infection control measures is applied in hospitals and postpartum nursing care centers to reduce the risk of EV clusters. Thus, there has been a marked decrease in severe and fatal EV cases during the last 10 years in Taiwan (23). A recent EV-A71 seroepidemiological study also supported the impact of a well-established real-time EV surveillance system and the preventive measures to limit the spread of EV-A71 in Taiwan (24). For example, the EV-A71 seropositive rate of adolescents aged 12–19 years decreased from 65% in 1997 to 46% in 2017 (24). Therefore, the decreasing trend in the incidence of EV infection, either mild or severe, may be correlated with the decreasing trend of T1D incidence in Taiwanese adolescents.

In addition to epidemiological studies, a pathological clinical study revealed that EV RNA was found in patients with diabetes more frequently than in control subjects and was associated with a clear inflammation response in the gut mucosa; additionally, patients remained virus positive in the follow-up samples taken after 12 months of observation (25). Another clinical cohort study found that the incidence of T1D increased after EV infection detected by the presence of blood viral RNA in genetically predisposed children who were repeatedly positive for islet autoantibodies (26). A systematic review and meta-analysis of observational molecular studies showed a strong association between T1D and EV. Significant associations between EV infection and T1D-

related autoimmunity and clinical T1D were observed, with odds ratios of 3.7 (95% CI 2.1–6.8) and 9.8 (95% CI 5.5–17.4), respectively (27). This study showed that the HR of T1D in children aged 0–6 years with EV infection was 1.46 (95% CI 1.35–1.58). Strong evidence exists for the association of EV infections with T1D in young children but not in those older than the age of 7 in this study.

In a recent large-cohort study of young children at an increased genetic risk, no difference was found in the EV infection rates between patients and subjects without diabetes, and prolonged shedding of EV-B was associated with islet autoimmunity but not T1D development (28). Several studies have indicated that EV infection may be an etiological agent or may accelerate pathogenesis because it may trigger the appearance of autoantibodies (26,29,30). By contrast, our study revealed that CVA was positively correlated with the incidence of T1D in children aged 0–6 years, but there was a striking lack of any association with EV beyond the age of 7. Moreover, we found that CVB was negatively correlated with the incidence of T1D in children aged 0–6 years, and it indicated that CVB in the Taiwanese population might be protective rather than pathogenic. Although statistical significance was not reached (r = −0.33; P = 0.224) (Table 2). This may implicate different endotypes of T1D in different age-groups and different populations.

The most frequently claimed virus to associate with T1D development was EV-B species or CVB species, but we did not have such findings. Why CVA, but not CVB, was positively correlated with the incidence of T1D in this study requires further investigation. The cause may be related to the higher incidence or circulation of CVA than that of CVB in Taiwan (23). According to the Taiwan CDC EV laboratory surveillance, CVA accounted for 26%–79%, and CVB only accounted for 0%–18% of all the serotypes between 2001 and 2015. In this study, the data taken from the Taiwan CDC are only representative of the most frequent serotypes in each species, and this is a limitation. Some studies have also revealed the association of CVA and

other serotypes of EVs with T1D (31–33). Hence, not only CVB but also CVA or other serotypes may be linked to T1D in children, and some inconsistencies exist among studies on EV and T1D.

Although this study had the strength of using longitudinal nationwide population data and long-term nationwide viral surveillance data, there were several limitations. First, the diagnosis of EV infection was based on the ICD-9-CM codes, which were mainly defined according to clinical phenotypes, leading to a question about accuracy. However, a special committee comprising medical and qualified experts regularly reviewed the charts and claims data to ensure the high reliability of the NHI database. Additionally, the high accuracy of other disease diagnoses in the NHI database was evaluated by other studies (34).

Second, the data taken from the Taiwan CDC are only representative of the most frequent serotypes in each species. Approximately 80% but not all the serotypes were analyzed.

Third, we could not identify the presymptomatic case subjects with T1D, and all of our case subjects had clinical phenotypes; thus, we could not analyze their endotypes and whether autoimmunity-related factors were associated with T1D. If the staging of T1D and endotype concepts are incorporated into laboratory and clinical practice, it will accelerate the implementation of precision medicine and may impact our approach to translational research, trial design, and clinical management (26,35).

Fourth, we did not have available data for EV RNA or antibodies against EVs in these children with T1D. Therefore, a prospective study to investigate CVA infection in children with T1D is necessary to establish their association or causal relationship.

In summary, the T1D incidence increased significantly in children aged 0–6 years, stabilized in children aged 7–12 years, and decreased significantly in adolescents aged 13–19 years from 2001 to 2015 in Taiwan. Children younger than 7 years with EV infection had a significantly higher risk of T1D and a positive correlation between T1D and CVA infection. The decreasing trend of the T1D incidence in adolescents may be related to genetic factors and environmental factors such as better infection control of EVs during the last 10 years in Taiwan.

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