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Type 1 Diabetes and Increased Risk of Subsequent Asthma

A Nationwide Population-Based Cohort Study

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Abstract: The association between type 1 diabetes mellitus (T1DM) and asthma remains controversial and has led to new interest in these 2 disorders. The purpose of this study was to examine the associations among young people with T1DM and asthma and offer a clinical demonstration of the balance between Th1 and Th2 responses.

We conducted a retrospective cohort study by using data from the National Health Insurance (NHI) system of Taiwan. The cohort consisted of 3545 T1DM cases and 14,180 controls established during the 1998 to 2011 period. Of the 3545 T1DM patients, 55.1% were girls and 26.5% were in the age group <8 years.

The overall incidence of asthma was 47% higher in the T1DM cohort than in the control cohort (6.49 vs 4.42 per 1000 person-y), with an adjusted hazard ratio (HR) of 1.34 (95% confidence interval [CI]=1.11–1.62). Moreover, T1DM patients who visited the emergency room (ER) more than twice for diabetes had a higher adjusted HR of 17.4 (95% CI = 12.9–23.6) of developing asthma. The adjusted HR of asthma was 38.6 (95% CI = 28.5–52.2) in T1DM patients who had been hospitalized more than twice for diabetes.

We observed a significantly higher incidence of asthma in young patients with T1DM than in the general population. Among young

people of T1DM with more ER visits or frequent hospitalization because of diabetes mellitus were associated with risk of asthma, may indicate that poor glycemic control significantly contributes to asthma risk.

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Abbreviations: CIs = confidence intervals, ER = emergency room, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID 2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, RCIPI = Registry of Catastrophic Illnesses Patient Database, T1DM = type 1 diabetes mellitus, Th = T helper type.

INTRODUCTION

Asthma is the most common chronic inflammatory illness in childhood and a major cause of morbidity in adults, affecting 9.3% of children in the United States¹ and 20.7% of school children in recent Taiwan epidemiological study (according to the Taiwan Association of Asthma Education²). International Study of Asthma and Allergies in Childhood (ISAAC) study showed the overall prevalence and rising trend of physician-diagnosed asthma in Taiwanese school significantly increased from 4.5% in phase I to 6.0% in phase III (prevalence odds ratio = 1.4, 95% CI 1.2–1.5).³ Asthma is characterized by a chronic inflammatory reaction mediated by T helper type 2 (Th2)-dominant cells. Another common chronic childhood-immune disease, type 1 diabetes mellitus (T1DM), is Th1-dominant, in which Th1 and Th2 cells reciprocally counteract each other and the balance between their responses provides a possible explanation.⁴ Several studies have also demonstrated an inverse relationship between asthma, atopic diseases, and the risk of developing T1DM.^{5,6} In Taiwan, a recent report conducted by pediatricians showed that patients with T1DM have lower prevalence of atopic symptoms than those without T1DM.⁷ However, a previous finding by Stene and Nafstad showed a strong positive association between the occurrence of T1DM and asthma at the population level in Europe.⁸ This unexpected finding led them to attempt to identify the risk factors and etiologies involved in these 2 disorders. Another recent study revealed asthma to be associated with an increased risk of diabetes mellitus (DM) (hazard ratio [HR] = 2.11; 95% confidence interval [CI] = 1.43–3.13; $P < 0.001$).⁹ The hygiene hypothesis suggests that lower microbial exposure in early life may contribute to increased prevalence of immune-mediated diseases, such as asthma and T1DM.^{10,11} The Th1 and Th2 secretory pattern of patients with T1DM and asthma combines features of both diseases, suggesting a unique Th1/Th2 balance, including a lower Th1/Th2 ratio compared with patients with T1DM only.¹² The relationship between asthma and T1DM among young people has not been thoroughly

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TABLE 1. Comparisons in Demographic Characteristics and Comorbidities in Patient With and Without Type 1 DM

	Controls (N = 14,180) n (%)	T1DM (N = 3545) n (%)	P value
Sex			0.99
Girl	7816 (55.1)	1954 (55.1)	
Boy	6364 (44.9)	1591 (44.9)	
Stratified by age			<0.001
≤ 8	2953 (20.8)	940 (26.5)	
>8	11,227 (79.2)	2605 (73.5)	
Age, mean ± SD*	12.4 (5.10)	11.3 (5.04)	<0.001
Urbanization†			0.05
1 (highest)	38,150 (26.9)	1000 (28.2)	
2	4266 (30.1)	1111 (31.3)	
3	2791 (19.7)	660 (18.6)	
4 (lowest)	3308 (23.3)	774 (21.8)	
Parental occupation			<0.001
White collar	8076 (57.0)	1954 (55.1)	
Blue collar	4404 (31.1)	1065 (30.0)	
Others	1700 (12.0)	526 (14.8)	
Comorbidity			
Atopic dermatitis	585 (4.13)	245 (6.91)	<0.001
Rhinitis	4902 (34.6)	1228 (34.6)	0.94
Hypertension	54 (0.38)	186 (5.25)	<0.001
Hyperlipidemia	57 (0.40)	798 (22.5)	<0.001
Depression	190 (1.34)	113 (3.19)	<0.001
Anxiety	150 (1.06)	155 (4.37)	<0.001

Chi square test. DM = Diabetes Mellitus, SD = Standard deviation.

* *t* test.

† 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 as the least urbanized.‡ Other occupations included primarily retired, unemployed, or low-income populations.

investigated. Positive glycemic control can prevent the onset of diabetic complications in children.¹³ How poor glycemic control or high hemoglobin A1c levels deteriorate into asthma remains unclear. The association between T1DM and asthma is controversial and has led to new interest in these 2 disorders. This study examined the associations among young people with T1DM and asthma and offers a clinical demonstration of the balance between Th1 and Th2 responses.

METHODS

Data Source

The Taiwan National Health Insurance (NHI) program offers comprehensive, universal health insurance to all residents of Taiwan since 1995. The NHI program covers >99% of the residents of Taiwan and is contracted with 97% of medical providers (<http://www.nhi.gov.tw/english/index.aspx>). The National Health Research Institutes (NHRI) was commissioned to construct and maintain the National Health Insurance Research Database (NHIRD) for researchers. The study patients were identified from 2 subsets of the NHIRD: the Registry of Catastrophic Illnesses Patient Database (RCIPD) and the Longitudinal Health Insurance Database 2000 (LHID 2000). The NHI program specifies 30 categories of catastrophic illness (eg, cancers, hemophilia, and autoimmune diseases, including type 1 diabetes). Eligible patients can apply for catastrophic illness certificates, and if approved, are exempted from copayment of related medical costs. Both outpatient and inpatient claims

of beneficiaries with a catastrophic illness certificate are collected in the RCIPD (http://www.nhi.gov.tw/webdata/webdata.aspx?menu=&menu_id=&wd_id=&webdata_id=3180). The LHID 2000 comprises detailed claims data of 1 million people randomly sampled from the population of Taiwanese in 2000. No significant difference exists in sex, age, or health care costs between cohorts in the LHID 2000 and all insureds in the NHIRD (http://w3.nhri.org.tw/nhird/date_01.html). Diagnostic codes were in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the Research Ethics Committee of China Medical University (CMUH-104-REC2-115). The patients were diagnosed of T1DM or asthma by clinical physicians and objective laboratory report.

Sampled Participants

The T1DM cohort was identified from the RCIPD, including patients in the age group of 1 to 20 years, newly diagnosed with T1DM (ICD-9-CM codes 250.x1 and 250.x3) between 1998 and 2011. The date of application for T1DM was defined as the index date. Patients suffering from asthma (ICD-9-CM code 493) or with missing age or sex information at the baseline were excluded. The control cohort was identified from the LHID 2000. For each T1DM case, 4 insureds without a history of T1DM or asthma were identified as the control cohort, frequency matched by age (in 10-y bands), sex, and index year. The same exclusion criteria were also applied to the control

TABLE 2. Comparison of Incidence Densities of Asthma and Hazard Ratio Between With and Without Type 1 DM by Demographic Characteristics and Comorbidity

	Controls			T1DM			Crude HR [†] (95% CI)	Adjusted HR (95% CI)
	Event	PY	Rate [#]	Event	PY	Rate [#]		
All ¹	416	94,188	4.42	153	23,568	6.49	1.47 (1.23, 1.77)***	1.34 (1.11, 1.62)**
Sex ²								
Girl	201	52,326	3.84	65	13,083	4.97	1.30 (0.98, 1.71)	1.40 (1.05, 1.88)*
Boy	215	41,861	5.14	88	10,485	8.39	1.64 (1.28, 2.10)***	1.52 (1.17, 1.97)**
Stratify age ³								
≤ 8	271	26,444	10.3	105	5861	17.9	1.49 (1.19, 1.86)***	1.52 (1.21, 1.91)***
>8	145	67,743	2.14	48	17,707	2.71	1.30 (0.94, 1.80)	1.56 (1.09, 2.22)*
Comorbidity ^{‡,4}								
No	165	59,694	2.76	64	9177	6.97	2.42 (1.81, 3.23)***	1.92 (1.44, 2.58)***
Yes	251	34,494	7.28	89	14,391	6.18	0.88 (0.69, 1.12)	0.97 (0.76, 1.24)
Follow-up time ¹								
≤1 years	117	13,548	8.64	63	3384	18.6	2.16 (1.59, 2.93)***	2.10 (1.54, 2.86)***
>1 years	299	80,639	3.71	90	20,183	4.46	1.21 (0.95, 1.53)	1.18 (0.92, 1.52)

*Rate, incidence rate, per 1000 person-years; †crude HR, relative hazard ratio; ‡comorbidity: patients with any one of the comorbidities atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety were classified as the comorbidity group. CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, PY = person-years.

¹Adjusted HR was calculated by Cox proportional hazard regression and adjusted for sex, age, urbanization, parental occupation, and comorbidities of atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety.

²Adjusted HR was calculated by Cox proportional hazard regression stratified by sex and adjusted for age, urbanization, parental occupation, and comorbidities of atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety.

³Adjusted HR was calculated by Cox proportional hazard regression stratified by age and adjusted for age, urbanization, parental occupation, and comorbidities of atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety.

⁴Adjusted HR was calculated by Cox proportional hazard regression stratified by comorbidity and adjusted for age and sex.

*P < 0.05; **P < 0.01; ***P < 0.001.

patients. The T1DM cohort comprised 3545 patients and the control cohort comprised 14,180 patients. The cumulative censoring rate >14 years (1998–2011) was 2.06% in the T1DM cohort, which was slightly lower than that in the control cohort (1.37%). The possible reasons for the discontinuity of National Health Insurance include death, withdrawal of insurance, immigration, prison sentence, and so on.

Outcome

Patients in both the T1DM and control cohorts were followed from the index date to the date of asthma occurrence or censoring because of loss of follow-up, withdrawal from the NHI program, or until the end of 2011.

Variables of Interest

Some sociodemographic variables including sex, age, urbanization level, and parental occupation were used in this study for further adjustment. The detailed definitions of urbanization level and parental occupation have been well described according to the previous publications.^{14,15} Certain important and potential risk factors were also included [atopic dermatitis (ICD-9-CM codes 691), rhinitis (ICD-9-CM codes 472.0 and 477), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2, 296.3, 300.4, 301.12, 309.0, 309.1, and 311), and anxiety (ICD-9-CM code 300)] to be the co-morbidities.

Statistical Analysis

The distribution of demographic data and comorbidities (sex, age, urbanization level, parental occupation, comorbidities

of atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety) were compared between the T1DM cohort and control cohort. Differences were examined using the chi-square test for categorical variables and Student's *t* test for continuous variables. The incidence densities (per 1000 person-y) were estimated according to sex, age, comorbidity, and

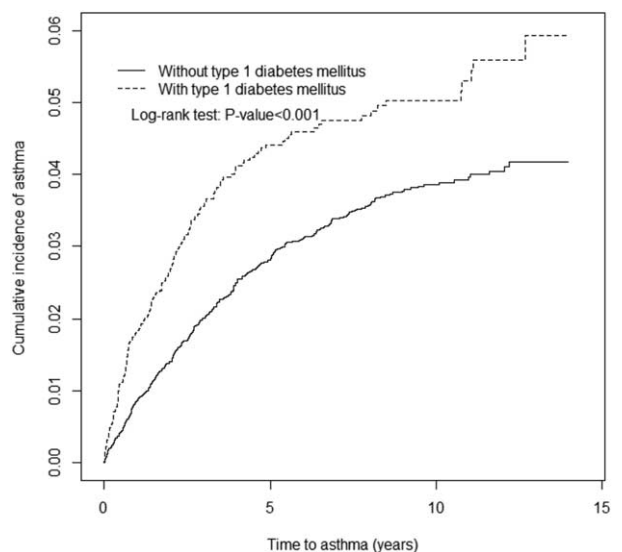


FIGURE 1. Cumulative incidence of asthma for patients with (dashed line) Type 1 DM or with (solid line) Type 2 DM. DM = Diabetes mellitus.

follow-up time in both the cohorts. Univariate and multivariate Cox proportional hazard regressions were used to compare the risk of developing T1DM-associated asthma in the T1DM cohort and control cohort. Variables in the multivariable model included age, sex, urbanization level, parental occupation, and comorbidities of atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety. The HR and 95% CI were estimated using the Cox model, which was also used to assess the association between asthma and the frequency of T1DM-related medical visits. The Kaplan–Meier method was used to plot the cumulative incidence of asthma between the 2 cohorts, and a log-rank test was used to compare the cohorts. All analyses were performed using the statistical package SAS for Windows (Version 9.3, SAS Institute Inc, Carey, NC).

RESULTS

The cohort consisted of 3545 T1DM cases and 14,180 controls established during the 2002 to 2011 period. Of the 3545 T1DM patients, 55.1% were girls and 26.5% were in the age group of <8 years (Table 1 Table 1). The mean ages of participants in the T1DM and control cohorts were 11.30 (±5.04) and 12.40 (±5.10) years, respectively. Both cohorts tended to reside in urbanized areas (59.5% vs 57.0%) and half of the participants’ parental occupations were classified as white-collar workers (55.1% vs 57.0%). The patients in the T1DM cohort tended to have a higher prevalence of atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety than those in the control cohort. The mean follow-up time for the T1DM and control cohorts was 6.65 (standard deviation [SD]=4.04) and 6.64 (SD=4.01) years, respectively. Figure 1 shows that the cumulative incidence of asthma was significantly higher in the T1DM cohort than in the control cohort (log-rank test, *P* < 0.001).

The incidence densities of asthma and the HR between the T1DM and control cohorts are shown in Table 2. The overall incidence of asthma was 47% higher in the T1DM cohort than in the control cohort (6.49 vs 4.42 per 1000 person-y), with an adjusted HR of 1.34 (95% CI = 1.11–1.62). The incidence of asthma was greater in boys than in girls in both cohorts. The gender-specific hazard of asthma in the T1DM cohort relative to

that in the control cohort was significant for both girls (adjusted HR = 1.40, 95% CI = 1.21–1.91) and boys (adjusted HR = 1.56, 95% CI = 1.09–2.22). The highest incidence of asthma was in T1DM patients < 8 years of age (17.9 per 1000 person-y). However, the adjusted HR of the age-specific T1DM patients to the control participants was the highest for all age groups (adjusted HR = 1.52, 95% CI = 1.21–1.91 for age ≤ 8 y; adjusted HR = 1.56, 95% CI = 1.09–2.22 for age > 8 y). Among the patients without comorbidity, the risk of asthma was 1.92-fold higher in the T1DM cohort than in the control cohort (95% CI = 1.44–2.58). The highest incidence of asthma was in T1DM patients in the first follow-up year (18.6 per 1000 person-y). The adjusted HR of asthma was significantly higher in the first follow-up year (adjusted HR = 2.10, 95% CI = 1.54–2.86).

Table 3 shows the incidence densities and HRs of asthma for T1DM patients associated with the frequency of emergency room (ER) visits and hospitalizations. Compared with the control cohort, T1DM patients with > 2 ER visits for their diabetes had a higher adjusted HR of 17.4 (95% CI = 12.9–23.6) for developing asthma. The adjusted HR of asthma was 38.6 (95% CI = 28.5–52.2) in T1DM patients who had been hospitalized more than twice for their diabetes.

DISCUSSION

T1DM is a heterogeneous disorder and one of the most common chronic diseases in childhood, characterized by absolute insulin deficiency following autoimmune-mediated destruction of pancreatic beta cells. Large epidemiologic studies have indicated that the incidence of T1DM has been increasing by 3% per year worldwide and that the estimated incidence rate is 6.4/100,000 for 0- to 9-year-old Asians and Pacific Islanders.¹⁶ The prevalence is ~ 1 in 300 in the United States, by 18 years of age.¹⁷ A progressive increase in the prevalence of T1DM and asthma has been noted in populations in developed countries. We attempted to identify the factors involved in these 2 disorders and to assess the increasing prevalence. A recent study has raised questions regarding a possible link between these 2 chronic illnesses and their treatments. A previous European study showed that the risk of asthma significantly decreased in children with T1DM, with

TABLE 3. Hazard Ratios and 95% Confidence Intervals of Asthma Risk Associated with the Number of Annual T1DM-Related Visit

	Asthma		Hazard Ratio (95% CI)	
	No. of Event	Rate [#]	Crude	Adjusted [†]
Controls	416	4.42	1 (Reference)	1 (Reference)
Times of emergency room visit for T1DM				
≤2	99	4.27	0.97 (0.78, 1.21)	0.98 (0.78, 1.23)
>2	54	136.7	25.0 (18.8, 33.2) ^{***}	17.4 (12.9, 23.6) ^{***}
<i>p</i> for trend			<0.001	<0.001
Times of admission for T1DM				
≤2	96	4.11	0.94 (0.75, 1.17)	0.93 (0.74, 1.18)
>2	57	249.4	42.6 (32.1, 56.6) ^{***}	38.6 (28.5, 52.2) ^{***}
<i>P</i> for trend			<0.001	<0.001

Rate[#], incidence rate, per 1000 person-years; crude HR^{*}, relative hazard ratio; adjusted HR[†]: multivariable analysis including age, sex, urbanization, parental occupation, and comorbidities of atopic dermatitis, rhinitis, hypertension, hyperlipidemia, depression, and anxiety. CI = confidence interval, T1DM = type 1 diabetes mellitus.
^{*}*P* < 0.05; ^{**}*P* < 0.01; ^{***}*P* < 0.001.

an odds ratio of 0.64 (95% CI = 0.51–0.82).¹⁸ Lancet revealed a negative association between asthma symptoms and T1DM, and that nondiabetic siblings are prone to the protective effect may be due to environmental factors encountered in early life or genetic risk factors.¹⁹ The protective mechanisms induced by infection are unknown but thought to be related to the production of regulatory T-cells. The complex interactions between the immune system components that balance the Th1/Th2-cell responses play a role in the development of either disease. The Th1 and Th2 secretory patterns of patients with T1DM and asthma combines features of both diseases, suggesting a unique Th1/Th2 balance of a lower Th1/Th2 ratio compared with patients with T1DM alone.¹² Animal studies have suggested that Th1 and Th2 cytokines can be expressed in the same Th cell simultaneously.²⁰ According to the cross-regulatory properties of Th1 and Th2 cells, we hypothesized that the 2 disorders overlap in patient populations. Previously, Th2 immune processes in the airways of people with asthma. Numerous factors may be involved in the development of non-Th2 asthma, including infection-related elements, Th1 and Th17 immunity, non-Th2-associated smooth-muscle changes including genetics and oxidative stress, and the development of neutrophilic inflammation. The asthma phenotype is a popular mechanism, and previous studies have described numerous asthma classifications based on age of onset, type of inflammation, and pattern of severity. Various phenotypes may be associated with T1DM in young people.

In our study, we observed a significantly higher incidence of asthma in patients with T1DM than in the general population (6.49 vs 4.42 per 1000 person-y; Table 2). Analyses indicated that T1DM-associated asthma risk was the highest in patients < 8 years of age (17.9 per 1000 person-y). A possible explanation may be that older patients tended to have more comorbidities, which may be risk factors for late-onset asthma. Moreover, T1DM patients with more ER visits or hospitalizations for diabetes were at higher risk for asthma, according to our results. A frequency of more than 2 annual visits (for T1DM) implied a higher HR of asthma risk compared with that of children without T1DM (adjusted HR = 17.4 [95% CI = 12.9–23.6] for ER visits, HR = 38.6 [95% CI = 28.5–52.2] for hospitalization, respectively; Table 3). In contrast, T1DM patients who had once or twice emergency room visits or hospitalizations did not seem to have increased risk of asthma compared with control group statically. Among T1DM patients, more emergency room visits or hospitalizations indeed increased risk of asthma. It may suggest that poor glycemic control was associated risk of asthma. Poor glycemic control that primes chronic inflammation may upset the balance between Th1/Th2 cell responses. A possible explanation for this finding is that T1DM-dominated Th1 cells mediated the shift to Th2 expression. These data demonstrate that Th1 and Th2 diseases can coexist. Current cross-sectional analysis from the SEARCH for Diabetes in Youth study conducted by Pediatrics 2011 on asthma and glycemic control indicated that the prevalence of asthma among all young people with T1DM was 10.0% (95% CI = 8.6–11.4%). Among young people with T1DM, those with asthma had higher mean hemoglobin A1c levels than did those without asthma.²¹ Several studies have demonstrated poorer pulmonary function among people with diabetes compared with nondiabetic controls.²² The existence of Th1-dominated disease does not reduce the incidence of asthma, indicating a common environmental factor behind the disease processes. A deficiency in microbial exposure may cause a reduced number of infections or delayed compositional development of the intestinal

microflora.²³ The hygiene hypothesis provides an explanation for these complex associations and proposes that infections in early childhood may reduce the risk of allergic diseases and induce the Th2 profile to move toward the Th1 phenotype.¹⁰ The decline of tuberculosis incidence could be related to rising rates of allergy and T1DM between tuberculin responses and atopic disorders in Japanese school children.²⁴

These 2 disorders may share risk factors. The body mass index (BMI) has been observed to have a crucial association with asthma risk among young people with T1DM,²¹ suggesting that they have concomitant asthma. Because the symptoms of early stage asthma are not prominent, clinical diagnosis may be difficult. The differences in diagnosis time of these 2 disorders might result in a gradual increase in the cumulative incidence of asthma for patients with T1DM compared with patients without T1DM.

However, we acknowledge some limitations in our study. First, the NHIRD does not contain detailed information regarding smoking habits, BMI, reproductive function, medical drug history, and family history of systemic diseases. Second, these data did not allow us to assess changes in asthma severity and the condition about glycemic control. Third, we could not list all the possible risk factors of asthma as confounders to adjust the HR between the T1DM group and the control group. However, Taiwan launched an NHI program operated by a single-payer, the government, in 1995. All insurance claims are scrutinized by medical reimbursement specialists and subject to peer review. Therefore, the data regarding the diagnoses for T1DM and asthma were reliable.

In conclusion, our study does not argue the hypothesis of the characteristic mutual inhibition of the Th1/Th2 immune system. However, our findings imply that general shifts in the Th1/Th2 balance at the population level are likely to be a major explanation of the change. Our patients with T1DM had a significantly higher risk of developing asthma than the control group did. A further study is required to clarify the pathophysiological mechanisms of T1DM and asthma.

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