

Decreased Risk of Influenza in Child and Adolescent Patients with Attention-Deficit Hyperactivity Disorder Following Methylphenidate Treatment: A Nationwide Cohort Study in Taiwan

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Background: Young individuals with attention-deficit hyperactivity disorder (ADHD) may have an elevated risk of influenza because of the difficulty in complying with the behavioral procedures that help protect against influenza. Moreover, the effects of sufficient methylphenidate treatment on influenza have received little attention.

Objective: This study evaluated the association between ADHD medication usage and influenza and assessed the effect of duration of ADHD treatment on the risk of influenza using a nationwide population-based database.

Methods: This study investigated methylphenidate usage and the risk of influenza among children and adolescents with ADHD. We identified 5259 young individuals aged less than 18 years who were diagnosed as having ADHD between 1996 and 2013 from the National Health Insurance Research Database of Taiwan, and we tested whether methylphenidate use affects influenza risk using Cox proportional hazard models.

Results: After controlling for confounding factors, the results indicated that influenza risk significantly reduced in the group of ADHD patients who were prescribed methylphenidate for 90 days and more (hazard ratio [HR]: 0.62, 95% confidence interval [CI]: 0.52–0.75, $p < 0.001$), demonstrating a 38% reduction in the risk of influenza in this group. However, this was not observed in the group of ADHD patients who used methylphenidate for 1–90 days (HR: 0.69, 95% CI: 0.89–1.05, $p = 0.12$).

Conclusion: The lower incidence of influenza observed in the group prescribed with methylphenidate for a longer period highlights the importance of compliance to medication and psychoeducation with regard to ADHD management.

Keywords: ADHD, influenza, methylphenidate

Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder and typically affects approximately 5–7% of the pediatric population irrespective of the geographical location or cultural background.^{1–3} People with ADHD typically demonstrate enduring hyperactivity, impulsivity, reduced attention, and increased distractibility that may span from childhood to adulthood and potentially impair everyday functioning.⁴ This disorder is associated with delayed social and emotional development,⁵ increased likelihood of self-harm and suicide attempts,^{6,7} increased risk of accident and injury,⁸ and high

family stress and healthcare utilization.⁹ Studies have indicated that pharmacological treatment, including stimulant medication or atomoxetine, can improve functional outcomes and health-related quality of life,^{10,11} and pharmacological treatment is associated with a lower rate of substance-related problems¹² and risk-related behaviors including suicide,^{13,14} injury^{15,16} and fracture.¹⁷ Another study of stimulant medications for the treatment of ADHD suggested that the medications can successfully decrease the risks of certain common psychiatric conditions, such as depression, anxiety, and personality disorder.¹⁸

Influenza is generally regarded as a severe illness only for elderly persons and those with chronic conditions that increase their risk of complications.¹⁹ However, during the novel 2009 H1N1 influenza pandemic, the highest incidence rates were recorded among children and young adults, with incidence rates exceeding 40% in preschool-aged children and 30% in school-aged children.²⁰ The burden of influenza on pediatric respiratory hospitalization is demonstrated by the rate of respiratory hospitalization attributed to influenza, which is 10% in children aged less than 18 years and 16% among children aged 5–17 years worldwide.²¹ Non-pharmaceutical behavior prevention of influenza and reduction of influenza virus transmission among children and adolescents involve practicing appropriate hand hygiene (frequent hand washing with hand wash products) and upholding respiratory hygiene,^{22,23} cough etiquette and social distancing.^{23–25} In addition, psychoeducation and awareness on the risk for influenza are emphasized.^{23,24}

Research has revealed that ADHD is associated with inflammatory and immune-related disorders (ie, atopic disorders including allergic rhinitis, asthma and eczema),^{26–28} suggesting a connection between psychopathology and inflammatory processes. One meta-analysis revealed that ADHD patients had increased rates of asthma.²⁹ Moreover, the odds of allergic rhinitis, eczema and allergic conjunctivitis in children with ADHD were found to be slightly higher than the non-ADHD group.²⁹ Although sufficient evidence has not been obtained to demonstrate that influenza is related to atopic diseases^{30,31} they have been recognized as predisposing factors for upper respiratory infections and symptom deterioration. In addition, the neurocognitive deficits associated with ADHD, for instance, difficulty following instructions and protocols or impulsive touching, which might hinder compliance with hand hygiene, could possibly lead to infectious diseases.³² In addition, a high percentage of children and adolescents with ADHD has nail-biting problems, which may also increase the risk of infections.^{33,34}

To the best of our knowledge, no study has investigated the relationship between the effect of ADHD medication usage toward the risk of influenza. Therefore, to bridge this gap in the literature, we evaluated the association between ADHD medication usage and influenza and the effect of duration of ADHD treatment on the risk of influenza using a nationwide population-based database.

Methods

Data Sources

Taiwan's NHI program was established by the government in March 1995, and this single-payer national health insurance program for healthcare delivery covered over 92% of the national population at that time. The government supported NHI program centralized healthcare utilizations, including inpatient, outpatient, and dental care. In 2009, the coverage of the NHI program increased to 99.5% of all medical claims. From the National Health Insurance Research Database of Taiwan (NHIRD-TW), the Bureau of NHI established a representative database of 1,000,000 people (ie, approximately 5% of the population of Taiwan) randomly sampled from the year 2005 registry of all NHI enrollees for research purposes, forming the Longitudinal Health Insurance Database (LHID). No statistically significant differences are observed in gender, age, or healthcare cost between the aforementioned LHID sample and all NHI enrollees.³⁵

Ethics

The LHID contains no identifying information. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

Study Population and Outcome Event

In this study, we identified 9826 patients newly diagnosed as having ADHD who either met criteria of DSM-IV³⁶ or DSM-IV-TR³⁷ within the follow-up period between January 31, 1996 and December 31, 2013. In this ADHD cohort, the diagnosis of ADHD was defined as follows: at least two outpatient records of ADHD within 1 year or at least one inpatient record of ADHD based on the International Classification of Diseases, Ninth Revision (ICD-9) code 314.³⁸ No significant difference was found for the incidence rate of influenza between sex-, age-, urbanization- and income-matched ADHD and non-ADHD cohorts.

Influenza was the outcome of this study and was operationalized according to ICD-9 codes 487 and 488.³⁸ Enrollees diagnosed as having influenza before the

diagnosis of ADHD ($n = 1786$) were omitted. Furthermore, the cohort identified from the database excluded those patients born before 1996 and after 2005 ($n = 2756$), and those with missing data on their residential area ($n = 3$), diagnosed as having ADHD in 2013 ($n = 271$), or receiving influenza vaccinations (code V04.8) 1 year before enrollment ($n = 68$). The flowchart of the criteria of inclusion and exclusion of this study is presented in Figure 1.

Methylphenidate Usage

The medications approved for ADHD treatment in Taiwan are methylphenidate and atomoxetine. Although atomoxetine, a nonstimulant, was approved in Taiwan in 2007,

pursuant to the Bureau of NHI guidelines, methylphenidate is the first choice of treatment for ADHD. Atomoxetine is only recommended for patients with ADHD who have unsatisfactory outcomes with methylphenidate, including poor response or intolerant side effects, or those who have concurrent conditions, including anxiety and tic disorder. In the LHID cohort, 4.3% of patients with ADHD were prescribed atomoxetine;³⁹ therefore, we limited our analysis to methylphenidate. The study cohort was divided into three groups according to the methylphenidate use duration (0 days, 1–90 days, >90 days); the duration was defined as the cumulative days of methylphenidate prescription during the follow-up period. The endpoint was defined as the occurrence of influenza or the end of the study period.

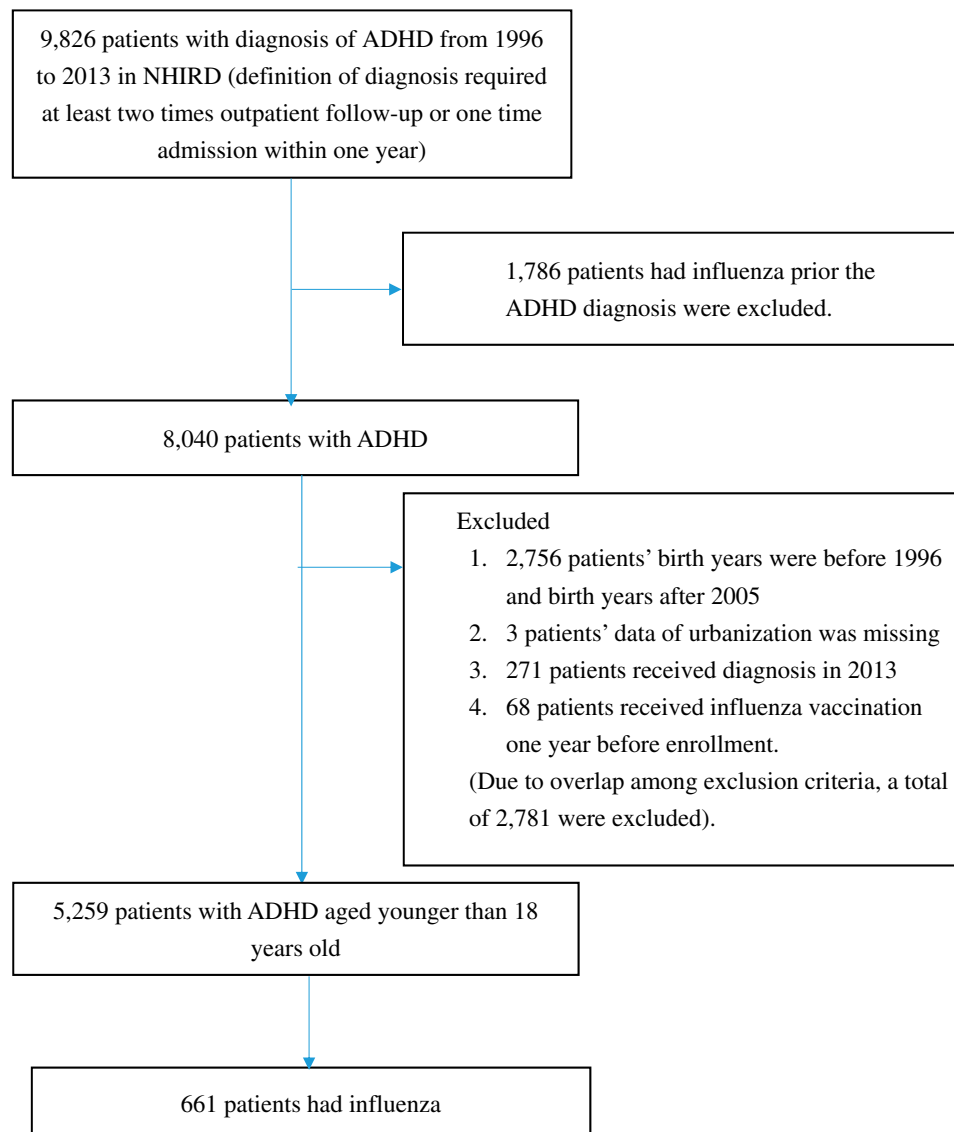


Figure 1 Flow diagram of criteria for inclusion and exclusion.

Statistical Analyses

First, using the chi-square test, we examined the differences in categorical variables among the groups with no methylphenidate use (0 days), methylphenidate prescription between 1 and 90 days (1–90 days), and methylphenidate use for more than 90 days (>90 days). Covariates identified from the ADHD and influenza literature were included in this study: gender, age, level of urbanization (from the most urbanized to the least urbanized), physical illness (asthma [ICD-9 code 493], atopic dermatitis [ICD-9 code 691], allergic rhinitis [ICD-9 code 477], and seizure [ICD-9 code 345]), psychiatric comorbidities (pervasive developmental disorder [ICD-9 code 299] and mental retardation [ICD-9 codes 317–319]), and use of medications (sedative/hypnotic/anxiolytics). Second, to investigate the risk of influenza within this ADHD cohort, a multivariate Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) while controlling for confounding factors and to compare the risk of influenza between the groups. Sensitivity analysis was performed in order to estimate the effect of longer duration (more than 180 days) usage of methylphenidate. A p value of ≤ 0.05 indicated statistically significant differences. The SAS software program Version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for data management and statistical analyses.

Results

Cohort Characteristics

We identified 5259 children and adolescents, of which 79% were male, with an incident ADHD diagnosis from the LHID between 1996 and 2013. Among this ADHD cohort, 2252 (42.8%) individuals with ADHD had not used any ADHD medication, while 3007 participants (57.2%) had used ADHD medication (1055 (20.1%) had used ADHD medication between 1 to 90 days and 1952 (37.1%) had used it for more than 90 days).

Of these, 661 (12.57%) children and adolescents had diagnoses of influenza during the follow-up period. Among them, 340 (51.43%) did not use methylphenidate, 124 (18.76%) used methylphenidate for less than 90 days, and 197 (29.80%) used methylphenidate for more than 90 days ($p < 0.001$). The detailed demographic data, comorbidities, and medication use are provided in [Table 1](#). In the groups with methylphenidate use, more patients tended to be male, older, and less urbanized compared with the

group without methylphenidate use. No significant differences were observed in physical or psychiatric illness and sedative/benzodiazepine/anxiolytic medication use among the three groups ([Table 1](#)).

Adjusted HRs of Influenza for Children and Adolescents with ADHD

[Table 2](#) presents the results of the fully adjusted Cox regression model after controlling for gender, age, level of urbanization, psychiatric or physical illnesses, and medication use (sedative/hypnotics/anxiolytics). The results indicate a statistically significant reduction in the incidence of influenza in patients with ADHD who were prescribed methylphenidate for more than 90 days (HR: 0.62, 95% CI: 0.52–0.75, $p < 0.001$). However, this was not observed in the group of ADHD patients who used methylphenidate for 1–90 days (HR: 0.69, 95% CI: 0.89–1.05, $p = 0.12$). An additional factor with a statistically significant association with the incidence of influenza was the comorbidity of allergic rhinitis (HR: 1.34, 95% CI: 1.04–1.73, $p = 0.021$). The cumulative incidence of influenza according to methylphenidate prescription is presented in [Figures 2 and 3](#).

Sensitivity Analysis

We also conducted a sensitivity analysis exploring the possible protective effects of a longer duration of methylphenidate prescription. The result of the sensitivity analysis revealed statically significant protective effects against influenza in the group with methylphenidate use for more than 180 days (HR: 0.61, 95% CI: 0.51–0.74, $p < 0.001$) as shown in [Supplement 1](#).

Discussion

To the best of our knowledge, the present study is the first to investigate the effect of psychostimulants and the moderating role of methylphenidate treatment duration on the risk of influenza among children and adolescents with ADHD. Our findings revealed that receiving methylphenidate treatment for more than 90 days was associated with an approximately 38% potentially reduction in the risk of influenza compared with no methylphenidate treatment. Furthermore, methylphenidate treatment duration shorter than 90 days did not reduce the risk of influenza.

Table I Characteristics of ADHD Youths with and without MPH Usage

Variables	MPH=0 d (N=2252)		MPH between 1 and 90d (N=1055)		MPH >90d (N=1952)		Chi-Square	P value
	Count	%	Count	%	Count	%		
Gender								
Male	1692	75.13	844	80.00	1619	82.94	39.2130	<0.001
Female	560	24.87	211	20.00	333	17.06		
Age (years)	6.76±2.68		8.03±2.57		7.66±2.44		275.2047	<0.001
0–5	779	34.59	155	14.69	302	15.47		
6–11	1342	59.59	794	75.26	1491	76.38		
12–18	131	5.82	106	10.05	159	8.15		
Levels of urbanization^a							29.5361	<0.001
1 (Most urbanized)	830	36.86	349	33.08	737	37.76		
2	1096	48.67	510	48.34	876	44.88		
3	245	10.88	121	11.47	220	11.27		
4 (Least urbanized)	81	3.60	75	7.11	119	6.10		
Covariates								
Seizure							2.4725	0.29
No	2180	96.80	1022	96.87	1874	96.00		
Yes	72	3.20	33	3.13	78	4.00		
Asthma							0.1533	0.926
No	1550	68.83	731	69.29	1339	68.60		
Yes	702	31.17	324	30.71	613	31.40		
Mental retardation							4.6313	0.099
No	2152	95.56	998	94.60	1837	94.11		
Yes	100	4.44	57	5.40	115	5.89		
ASD							0.2155	0.898
No	2159	95.87	1015	96.21	1874	96.00		
Yes	93	4.13	40	3.79	78	4.00		
Sedative/hypnotics/anxiolytics							2.5407	0.281
No	1608	71.40	740	70.14	1350	69.16		
Yes	644	28.60	315	29.86	602	30.84		
Atopic dermatitis							0.1415	0.932
No	900	39.96	419	39.72	769	39.40		
Yes	1352	60.04	636	60.28	1183	60.60		
Allergic rhinitis							0.6116	0.737
No	1177	52.26	538	51.00	1023	52.41		
Yes	1075	47.74	517	49.00	929	47.59		
Influenza							24.6388	<0.001
No	1912	84.90	931	88.25	1755	89.91		
Yes	340	15.10	124	11.75	197	10.09		
Follow-up Years	5.16±3.27		4.75±3.07		5.53±2.86			<0.001

Note: ^aResidential area are subgrouped by urbanized level.

Abbreviations: ASD, autism spectrum disorder; MPH, methylphenidate.

Table 2 Cox's Proportional Hazards Model for Influenza in ADHD Youths

Variables	Frequency		Univariate			Multivariate		
	Count	%	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Gender								
Male	4155	79.01	1.08	0.90~1.31		1.12	0.92~1.36	0.41
Female(ref.)	1104	20.99	1.00			1.00		0.25
Age (years)	7.35±2.63							
0-5(ref.)	1236	23.50	1.00			1.00		
6-11	3627	68.97	0.85	0.72~1.00	0.05	0.86	0.72~1.02	0.08
12-18	396	7.53	0.61	0.36~0.99	0.04	0.62	0.38~1.01	0.06
Levels of urbanization^a								
1 (ref.) (Most urbanized)	1916	36.43	1.00			1.00		
2	2482	47.20	1.03	0.87~1.21	0.767	1.04	0.88~1.23	0.66
3	586	11.14	1.02	0.78~1.32	0.89	1.05	0.81~1.37	0.71
4 (Least urbanized)	275	5.23	1.27	0.91~1.78	0.16	1.40	1.00~1.94	0.05
MPH usage								
0 day(ref.)	2252	42.82	1.00			1.00		
1-90 days	1055	20.06	0.83	0.68~1.02	0.08	0.85	0.69~1.05	0.12
>90 days	1952	37.12	0.62	0.52~0.74	<0.001	0.624	0.52~0.75	<0.001
P for trend test								<0.001
Covariates								
Seizure								
No(ref.)	5076	96.52	1.00			1.00		
Yes	183	3.48	1.14	0.78~1.66	0.50	1.12	0.76~1.65	0.56
Asthma								
No(ref.)	3620	68.83	1.00			1.00		
Yes	1639	31.17	1.34	1.14~1.57	<0.001	1.18	0.97~1.44	0.09
Mental retardation								
No(ref.)	4987	94.83	1.00			1.00		
Yes	272	5.17	0.75	0.51~1.11	0.15	0.79	0.53~1.17	0.24
ASD								
No(ref.)	5048	95.99	1.00			1.00		
Yes	211	4.01	0.92	0.63~1.34	0.66	0.937	0.64~1.38	0.74
Sedative/hypnotics/anxiolytics								
No(ref.)	3698	70.32	1.00			1.00		
Yes	1561	29.68	1.10	0.93~1.29	0.26	1.07	0.90~1.26	0.45
Atopic dermatitis								
No(ref.)	2088	39.70	1.00			1.00		
Yes	3171	60.30	1.38	1.17~1.61	<0.001	1.02	0.76~1.36	0.92
Allergic rhinitis								
No(ref.)	2738	52.06	1.00			1.000		
Yes	2521	47.94	1.41	1.21~1.64	<0.001	1.34	1.04~1.73	0.02

Note: ^aResidential area are subgrouped by urbanized level.

Abbreviations: ASD, autism spectrum disorder; MPH, methylphenidate.

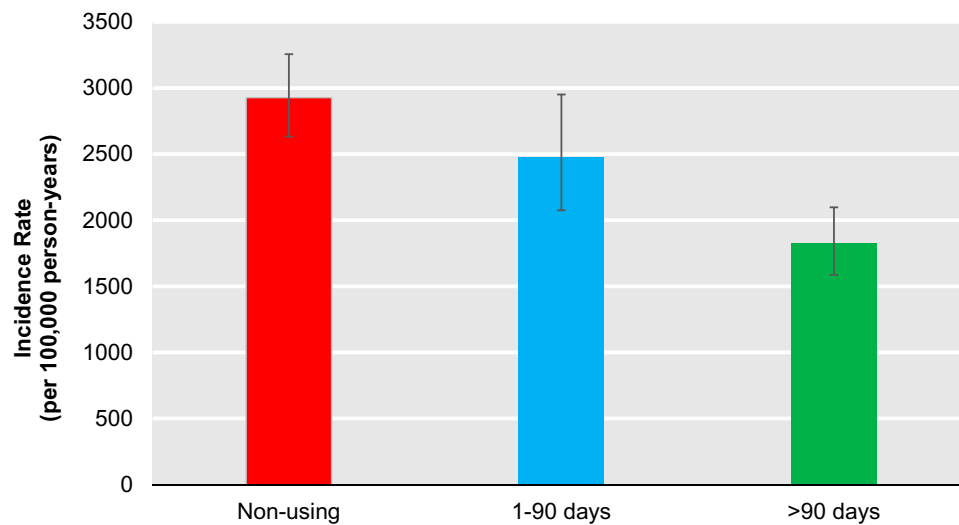
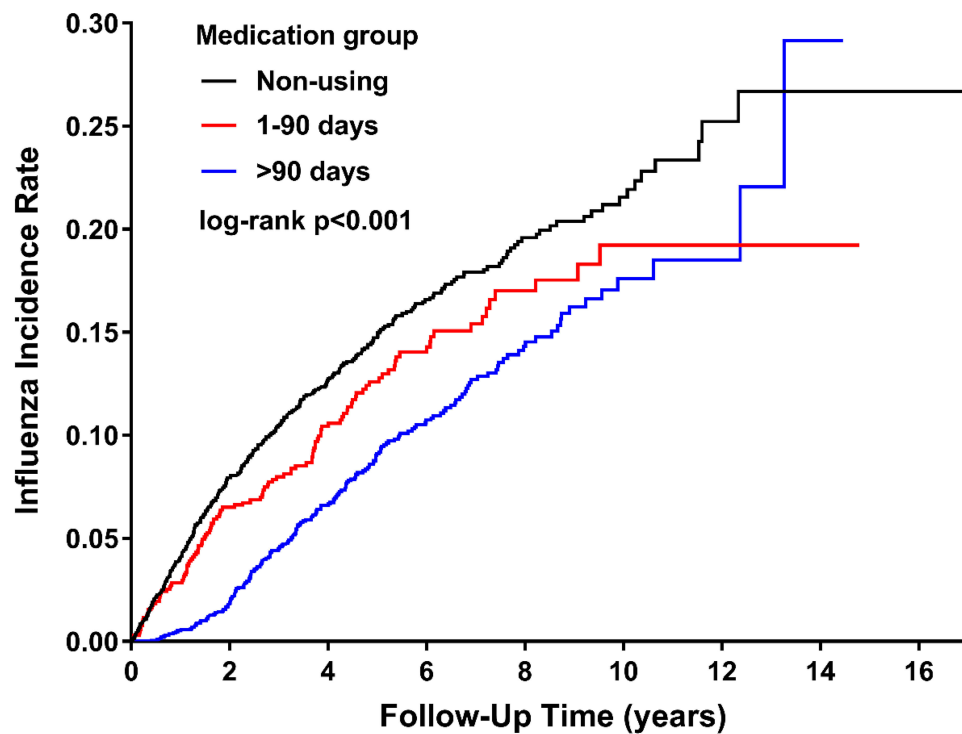


Figure 2 Incidence rates of influenza according to medication status in 5259 ADHD youths in Taiwan.^a

Note: ^aError bars indicate 95% confidence intervals.



Gray's Test for Equality of Cumulative Incidence Functions

Chi-Square	DF	Pr > Chi-Square
29.2667	2	<.0001

Figure 3 Cumulative incidence functions of influenza according to medication status in 5259 ADHD youths in Taiwan.

Duration of Methylphenidate Use and Influenza Risk

No study has explored either the risk of ADHD for influenza nor the association between ADHD treatment and the incidence of influenza; therefore, we cannot compare our results with any study. We conduct a sensitivity analysis to explore whether ADHD is a risk factor for influenza in children and adolescents in this LHID. Although there was no statistical difference between children and adolescents with ADHD and without ADHD, the ADHD group showed slightly increased risk of influenza compared to the non-ADHD group (incidence rate of ratios, IRR=1.04; 95% CI 0.98 1.11, $p=0.21$). Future study is suggested to exam the association between ADHD and influenza.

In our study, we found the longer ADHD treatment in youths with ADHD potentially decreased the risk of influenza. At the individual level, influenza prevention involves self-protective behaviors, including hand hygiene and respiratory hygiene/cough etiquette, and these might be more easily achieved during ADHD treatment.^{40,41} In addition to the possible decrease in the severity of core ADHD symptoms, proper social distancing²⁵ in conjunction with improved interpersonal, psychological, social, and educational functioning as well as improved health-related quality of life¹¹ may also partly underlie this protective effect.

Catecholamines and the Immune System

Oades et al reported that elevated interleukin (IL) levels in medicated children with ADHD tended to decrease within the normal range, indicating that minor immunological system imbalances improved following medication.⁴² Another possible mechanism for the reduction in influenza risk caused by methylphenidate use comprises stress-modulated immune responses through the hypothalamus–pituitary–adrenal axis and sympathetic nerve system.^{43,44} Several studies have suggested that the release of catecholamines (epinephrine and norepinephrine) during stress may induce immune protection, which accelerates wound healing and enhances metabolic rates and resistance to infections.^{43,44} Bigler et al reported that methylphenidate induces the recruitment of natural killer (NK) cells owing to increased epinephrine levels.⁴⁵ Their result suggested that the epinephrine-dominant stress response might promote immunological responses to induce the maturation of NK cells in peripheral circulation.

Research has described how NK cells identify influenza-infected cells with NKp44 and NKp46 receptors and help release cytotoxic enzymes to lyse these infected cells.⁴⁶ It is also plausible that the reduction in the risk of influenza associated with methylphenidate use is associated with the role of NK cells against viral infection or replication. Additional studies are warranted to explore this possible biological mechanism.

Allergic Rhinitis and Influenza

In our study, patients with allergic rhinitis also had an increased tendency of contracting influenza. Abnormal immune responses to viral infections in patients with chronic respiratory illnesses such as allergic rhinitis and asthma have been detailed.^{47,48} Such infection, via synergistic effects with Th2-related allergic inflammation, potentially plays a role in the initiation and exacerbation of allergic rhinitis and asthma. Direct aggravation of airway impairment as a result of heightened sensitivity and through indirect immunopathologic responses of respiratory mucosal immunity represents two mechanisms through which viruses may affect the respiratory tracts of asthmatics.⁴⁹

Moreover, high associations between ADHD and atopic diseases (ie allergic rhinitis, asthma and eczema) have been reported.^{26–28} For instance, a study revealed higher serum concentrations of various proinflammatory cytokines as well as IL-2, IL-6, IL-10, IL-13, IL-15, and interferon gamma in patients with ADHD compared with those in controls.²⁶ Further research on the associations between ADHD, atopic diseases, and influenza is warranted.

Strengths and Limitations

Strengths

The strengths in this study encompass the nationwide sample, the longitudinal cohort study nature, the clinic-based diagnosis of ADHD, explicit drug information, and varied dimensional covariates considered, together with sociodemographic, mental health factors, general health condition, and other medication use. In addition, high validity has been reported for the clinical diagnosis of ADHD in the LHID.³⁵ Both selection bias and recall bias were diminished by the use of this longitudinal population-based database.

Limitations

First, this study had considerable limitations relating to the lack of other personal information associated with

the risk of influenza, such as the individual's body weight, compliance to methylphenidate use, efficacy of psychoeducation, or behavior therapy as well as personal hygiene, such as hand washing, or respiratory hygiene for influenza prevention. Second, given that the prescription of atomoxetine for ADHD is rare in Taiwan (4.3%),³⁹ we only included patients who were prescribed methylphenidate and excluded those taking atomoxetine or a combination of methylphenidate and atomoxetine. However, our sensitivity analysis including patients who used atomoxetine revealed a similar protective effect for atomoxetine. Third, Taiwan's seasonal influenza vaccination program conducted by the Taiwan Centers for Disease Control commenced in 1998 and continued to be implemented in subsequent years.⁵⁰ In 2013, although the seasonal influenza vaccination coverage was up to 71.98% in primary school students,⁵¹ the status of vaccination is not fully recorded in the NHIRD-TW because data of those who received the vaccination through in-school influenza vaccination programs (for school-aged children between 7 and 15 years) and through self-paid influenza vaccinations in hospitals are not included. Therefore, we were unable to identify the immunization status of all study patients.

One possible explanation for the absence of a risk-reduction effect in young individuals with ADHD who did not receive methylphenidate treatment or who received methylphenidate treatment for less than 90 days may relate to nonadherence to ADHD medication and the reduced vaccination rate among the children of certain parental groups. Gau et al revealed that higher parental education (college or above) increased the risk of poor adherence to ADHD medication in Taiwan.⁵² One study in Brazil indicated that the vaccination coverage decreased among children in the highly educated class in some of Brazil's urban centers, indicating a shift from vaccination accessibility to vaccination acceptability regarding vaccine endorsement, particularly among those from highly educated families.^{53,54} Therefore, we infer less influenza vaccination coverage among non- or less medicated young individuals with ADHD in Taiwan, which may be a risk factor for the incidence of influenza.

Conclusions

The present study was based on data from a nationwide population-based database and revealed a reduction of influenza risk in children and adolescents with ADHD who were prescribed methylphenidate for periods

exceeding 90 days. This protective effect was not observed among those who used methylphenidate for less than 90 days. These results indicated that prescribing the appropriate ADHD medication and improving long-term pharmacological compliance may not only reduce the core symptoms of ADHD but also reduce the risk of influenza infection. Finally, the findings point to the importance of complying with medication, including the usage duration, for individuals prescribed with stimulants for ADHD treatment.

Abbreviations

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; NHIRD-TW, National Health Insurance Research Database of Taiwan; LHID, Longitudinal Health Insurance Database; HR, hazard ratio; CI, confidence interval; MPH, methylphenidate; IL, interleukin.

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Disclosure

VCHC has been an investigator in a clinical trial from Orient Pharma. SHYL has received speaking honoraria from Eli Lilly and Janssen. The authors report no other conflicts of interest in this work.

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