Association between Attention Deficit Hyperactivity Disorder Medication and Depression: A 10-year Follow-up Self-controlled Case Study

Yunhye Oh[1,2], Yoo-Sook Joung[1], Jinseob Kim[3]

[1]Department of Child and Adolescent Psychiatry, National Center for Mental Health, [2]Department of Psychiatry, Samsung Medical Center, Sungkyunkwan University School of Medicine, [3]Department of Epidemiology, School of Public Health, Seoul National University, Seoul, Korea

Objective: There is clinical concern that the stimulant methylphenidate (MPH) might increase the risk of depression, particularly in children. This study aimed to investigate the association between MPH use and the risk of depression. **Methods:** A population-based electronic medical records database was used. We obtained claims data for prescription of ADHD medication, diagnosis of depression, and prescription of antidepressant medication between January 2007 and December 2016 for 43,259 individuals aged 6 to 19 who were diagnosed with ADHD between July 1, 2007 and December 31, 2007. The final analysis was based on 2,330 eligible participants. A self-controlled case series design was used to identify risk factors for major depressive disorder (MDD). **Results:** An elevated MDD risk was found during the 90 days before MPH exposure, with an incidence rate ratio (IRR) of 12.12 (95% confidence interval [95% CI]: 10.06−14.61, p < 0.0001). During methylphenidate treatment, the IRR was 18.06 with a 95% CI of 16.67 to 19.56 (p < 0.0001), but it returned to baseline levels after day 31 of MPH treatment discontinuation. The IRR for patients aged 6 to 9 years was 13.11 (95% CI: 9.58−17.95) during the 90 days before MPH exposure, and 17.7 (95% CI: 15.6−20.08) during MPH treatment, but returned to baseline levels after discontinuation of MPH treatment. **Conclusion:** We confirmed the temporal relationship between depression and methylphenidate use in young people with ADHD. Though the absolute risk is low, the risk of depression should be carefully considered, particularly in the period directly following the start of methylphenidate treatment.

KEY WORDS: ADHD; Methylphenidate; Depression; Self-controlled case study.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children, with a world prevalence rate of approximately 5−7% [1-3]. ADHD is associated with various mental health and psychosocial adverse outcomes [4,5]. In particular, comorbid depression in youth with ADHD is relatively common [6], with a comorbidity rate of about 20% [7].

The American Academy of Child Adolescent Psychiatry recommends psychostimulants as primary medications for ADHD [8]. Over the past two decades, the use of ADHD medications has increased dramatically worldwide [9-11]. In Korea, the rate of ADHD medication prescription increased by 26% over four years, from 0.53% in 2007 to 0.72% in 2011 [12]. Methylphenidate is a first-line ADHD drug that has been proven to be safe and efficacious [13]. The European Medicine Agency reported in 2009 that the use of methylphenidate could worsen depression and suicidal ideation [14].

The association between methylphenidate and depression is controversial [15,16]. Several animal studies have reported that, due to the potency of MPH for stimulation, early exposure to MPH results in depressive-like behavior and reduces response sensitivity [17,18]. Limbic dysfunction due to chronic exposure to cocaine, a type of psycho-

stimulant, is associated with depression [17]. However, studies on the association between MPH and depression in humans are limited, and further longitudinal studies on human subjects are needed.

A recent large population-based cohort study demonstrated that MPH use decreases the risk of long-term and concurrent depression [19]. That study has the advantage of targeting 8−46 years 32,000 Swedish ADHD patients. However, the criteria for MPH exposure were oversimplified in the study design. For example, the groups were divided according to MPH prescription on January 1, 2006, and the risk of depression among the groups was compared. The researchers also followed up on depression for one year, from January 1 to December 31, 2009, a relatively short period of time. It also has the disadvantage of not considering each individual factor that may affect the occurrence of depression as a potential confounding factor. In another Swedish register-based longitudinal study of individuals 10−46 years showed positive association between MPH treatment and suicide-related events [20]. A previous study of youth 6−25 years also reported a 4-fold higher risk of suicide attempts during the first 90 days of methylphenidate treatment (incidence rate ratio [IRR], 3.91; 95% confidence interval [95% CI], 1.62−9.42), although the risk of suicide attempts was 6.5-fold higher during the 90-day period before methylphenidate initiation [21].

In South Korea, the Health Insurance and Review Assessment (HIRA) data are health insurance claims data that have been publicly released for research since 2009 [22]. The health insurance database is the standardized diagnosis code lists for a given population, as it provides complete records of all health care utilization information. These features also enable the assessment of a nationwide source of information regarding the use of health care resources during ADHD treatment. Therefore, using the HIRA database, a large population-based study is possible to explore the occurrence of depression caused by ADHD medication in the ADHD group. Therefore, the association between MPH medication use and depression remains unclear. This study aimed to identify the association between methylphenidate and depression retrospectively using a nationwide health insurance-based database.

METHODS

Data Source

We used medical claims data from the nationwide Health Insurance Review and Assessment Service (HIRA) database, which is based on data from the universal health insurance system in South Korea. The national health insurance system in South Korea covers all health services for approximately 50 million Koreans, almost 98% of the total population of South Korea; approximately 80,000 healthcare service providers are required to submit individual medical records to the database [22]. The claims database contains healthcare utilization information including demographics, prescription history, and diagnosis based on the International Classification of Diseases, 10th revision (ICD-10) [23]. HIRA data have been well validated and evaluated in previous reports [24,25]. We obtained claims data from January 1, 2007 to December 31, 2016 for patients aged 6 to 19 who had received a diagnosis of ADHD (ICD-10 codes F90) between July 1, 2007, and December 31, 2007. Patient-specific HIRA data representing personal identification were anonymized. The study protocol was approved by the Institutional Review Board of the National Center for Mental Health in Seoul, South Korea (IRB No.116271-2017-27).

Self-Controlled Case Series Design

We conducted a self-controlled case series (SCCS) study to determine the incidence of depression in children during periods in which they were exposed to methylphenidate compared with the incidence in periods in which they were not exposed. In an SCCS study, individuals act as their own controls [26]. This within-person study design enables comparisons in a population of individuals who have both the adverse event and exposure of interest, and is particularly useful when limited information is available on potential confounders [27]. The major strength of the SCCS design is that it adjusts for potential measured and unmeasured constant confounders that vary between individuals (i.e., genetic factors, disease severity, and socioeconomic factors) [28]. We also adjusted for time-varying factors such as age.

Case Identification

We extracted data on children 6 to 19 years of age who

had received a diagnosis of ADHD (ICD-10 code F90) between July 1, 2007 and December 31, 2007, and who were prescribed methylphenidate at least once during the observation period (July 1, 2007 to December 31, 2016). Depression was identified with the ICD-10 diagnostic codes F20 to F30.

We excluded subjects with ADHD who were diagnosed with major depressive disorder (MDD) between January 1, 2007 and June 30, 2007. We also excluded subjects who were treated with atomoxetine at least once to rule out a possible related risk of MDD. A flowchart indicating the selection of participants from the HIRA database for inclusion is displayed in Figure 1.

Exposures and Outcomes

The index date was defined as the first date of prescription of methylphenidate recorded in the HIRA database. We calculated the length of exposure using information on prescription date and number of prescribed days in the database. Patients contributed to consecutive exposure risk periods when they were continuously exposed to MPH. The post-exposure period of MPH was divided into 3 sub-periods: 1−30 days, 31−60 days, and 61−90 days after termination of MPH medication. All remaining time (outside the pre-exposure, exposure, and post-exposure periods) was considered to be unexposed time. Figure 2 shows how we classified the observation period for an individual participant with respect to exposure. The outcome was a new diagnosis of depression for which an antidepressant medication was prescribed. Depression events were defined as a recorded diagnosis (primary or secondary) of depression (codes F32, F33) treated with antidepressants. To ensure accurate diagnoses, we defined depression events as a recorded diagnosis of MDD
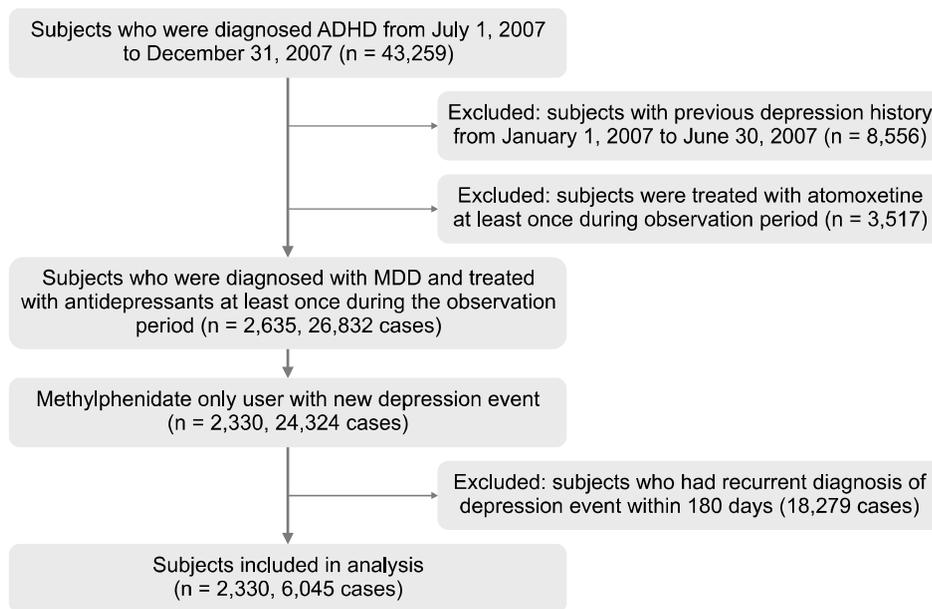

Fig. 1. Selection of study participants from national health insurance database in self-controlled case series design in children and young people with ADHD and depression.
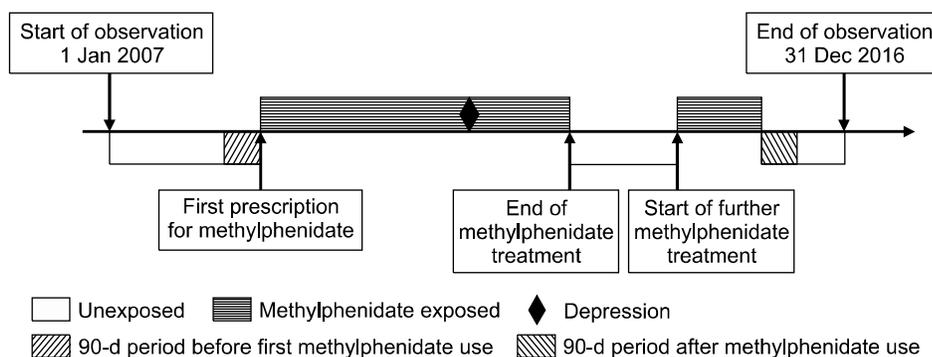MDD, major depressive disorder; ADHD, Attention Deficit Hyperactivity Disorder.

Fig. 2. Illustration of the self-controlled case series study design.

(F32−33) and prescription of antidepressant medication at least once in the HIRA database. We excluded any recurrent diagnosis of a depressive event within 180 days and included only the first event to avoid artificially inflating the risk of depression.

Statistical Analysis

We determined the duration of MPH exposure during the study period and the estimated incidence rate of MDD in each of the exposure risk periods after the start of MPH medication. The IRRs in periods of exposure to MPH compared with unexposed periods were calculated using conditional Poisson regression and adjusted for age and sex. We estimated the MDD-adjusted IRRs and their 95% CIs for exposure overall and during each predefined exposure risk period. Since this study only includes data from 2007 onwards, it may be difficult to rule out the possibility of recurrence of previous depression before 2007. Therefore, the authors performed additional subgroup analysis of children between 6 and 9 years of age, who were relatively young and, thus, less likely to develop depression. In order to consider the possibility that the disease burden may differ depending on the period from ADHD diagnosis to MPH use, further analysis was performed on the subgroup that initiated MPH within 3 years after ADHD diagnosis and the subgroup that used MPH within 1 year after diagnosis. The statistical application programs SAS (enterprise 6.1) and R version 3.3.1 (R foundation) were used for all statistical analyses.

RESULTS

In total, 43,259 individuals were diagnosed with ADHD between July 1, 2007 and December 31, 2007. To include only subjects with newly developed MDD after prescription of MPH medication, we excluded the 8,556 subjects who had been diagnosed with MDD between January 1, 2007 and June 30, 2007. We also excluded 3,517 subjects who were treated with atomoxetine at least once to rule out any possible influence on the risk of MDD. After those exclusions, 2,635 patients (2.65%) were diagnosed with MDD and treated with antidepressants at least once during the observation period (July 1, 2007 to December 31, 2016). Of those patients, 2,330 subjects were prescribed MPH at least once during the observation period.

Table 1 gives demographic details of the subjects included in our study. Regarding sex, 1,818 (78%) subjects were male. The median (interquartile range, IQR) age at diagnosis of ADHD was 10 (8−13) years, while median (IQR) age at MPH exposure was 11 (9−14) years. The median (IQR) age at first MDD event was 14 (12−17) years, and the median (IQR) duration of exposure of MPH was 1.20 (0.34−3.27) years. Table 1 also shows demographic details of the subgroup of children aged 6 to 9 years who were diagnosed with ADHD. Nine hundred twenty-one subjects had a recorded diagnosis of ADHD. The median age at first recorded ADHD diagnosis was 8 years, and the median age at first MDD event was 12 years. The median duration of exposure before events was 2.03 years.

The analysis indicated an association between use of

Table 1. Subjects characteristics

Variable	Total (n = 2,330)	Age 6 to 9 years (n = 921)
Sex, male	1,818 (78)	734 (79.7)
Exposure duration (yr)	1.20 (0.34, 3.27)	2.03 (0.68, 4.58)
Duration of MPH exposure before 1st MDD event (yr)	0.45 (0.04, 1.58)	0.73 (0.09, 2.13)
Duration of MPH exposure after MDD diagnosis (yr)	0.28 (0.00, 1.30)	0.55 (0.06, 2.11)
Age at MPH exposure (yr)	11.00 (9.00, 14.00)	9.00 (7.00, 10.00)
Age at ADHD diagnosis (yr)	10.00 (8.00, 13.00)	8.00 (7.00, 9.00)
Age at MDD diagnosis (yr)	14.00 (12.00, 17.00)	12.00 (10.00, 15.00)
No. of outpatient visit (n)	146.00 (95.00, 214.00)	170.00 (117.00, 233.00)
No. of psychiatric outpatient visit (n)	51.00 (24.00, 91.00)	62.00 (33.00, 101.00)
MPH prescription duration at each visit	23.33 (14.44, 30.15)	25.02 (16.17, 31.65)
Antidepressant use (d)	105.00 (35.00, 280.00)	116.00 (42.00, 321.00)

Values are presented as number (%) or median (interquartile range).
MPH, methylphenidate; MDD, major depressive disorder; ADHD, Attention Deficit Hyperactivity Disorder.

MPH medication and MDD. After adjusting for age, the IRRs were calculated by comparing the rate of events during exposed periods with the rate during unexposed periods. As shown in Table 2, we found an increased MDD risk during the 90 days before MPH exposure (IRR: 12.12; 95% CI: 10.06−14.61, $p < 0.001$). During the MPH-exposed period, the IRR was 18.06 (95% CI: 16.67 −19.56, $p < 0.001$). After MPH treatment discontinuation, the IRR decreased for the first 30 days (IRR: 2.56; 95% CI: 1.92−3.42, $p < 0.001$) and then returned to baseline levels by 31 to 60 days after MPH treatment discontinuation (IRR: 1.12; 95% CI: 0.72−1.74, $p = 0.618$). During the period from 61 to 90 days after MPH treatment discontinuation, the IRR slightly increased (IRR: 1.75;

95% CI: 1.21−2.51, $p = 0.003$). Age was associated with an increased risk of MDD (IRR: 1.58; 95% CI: 1.56−1.61, $p < 0.001$).

In the young age group, the IRR increased in the 90 days before MPH exposure (IRR: 13.11; 95% CI: 9.58− 17.95, $p < 0.001$). After prescription of MPH, the IRR was 17.7 (95% CI: 15.6−20.28, $p < 0.001$), and it returned to baseline levels by 1 to 30 days after MPH treatment discontinuation (IRR: 1.68; 95% CI: 0.98−2.86, $p = 0.058$). Age was associated with an increased risk of MDD (IRR: 1.54; 95% CI: 1.51−1.58, $p < 0.001$).

Table 3 demonstrates demographic characteristics of the subgroups of children who were initiated MPH within 3 years after ADHD diagnosis. The results showed a sim-

Table 2. Results from the self-controlled case series analyses

Risk period	No. of events	IRR (95% confidence interval)	p value
Total			
Unexposed	1,911	1	
Pre exposed: 90 d	134	12.12 (10.06−14.61)	< 0.001
Exposed	3,902	18.06 (16.67−19.56)	< 0.001
After exposed: 30 d	48	2.56 (1.92−3.42)	< 0.001
After exposed: 31−60 d	20	1.12 (0.72−1.74)	0.618
After exposed: 61−90 d	30	1.75 (1.21−2.51)	0.003
Age		1.58 (1.56−1.61)	< 0.001
Age 6 to 9 years			
Unexposed	529	1	
Pre exposed: 90 d	48	13.11 (9.58−17.95)	< 0.001
Exposed	2,044	17.7 (15.6−20.08)	< 0.001
After exposed: 30 d	14	1.68 (0.98−2.86)	0.058
After exposed: 31−60 d	7	0.92 (0.44−1.94)	0.826
After exposed: 61−90 d	10	1.42 (0.75−2.65)	0.279
Age		1.54 (1.51−1.58)	< 0.001

Table 3. Characteristics of subjects with subgroup analysis

Variable	MPH start within 1 years after ADHD diagnosis (n = 625)	MPH start within 3 years after ADHD diagnosis (n = 789)
Sex, male	502 (80.3)	634 (80.4)
Exposure duration (yr)	2.31 (0.84, 4.94)	2.34 (0.82, 5.06)
Duration of MPH exposure before 1st MDD event (yr)	1.00 (0.27, 2.57)	0.91 (0.17, 2.46)
Duration of MPH exposure after MDD diagnosis (yr)	0.51 (0.04, 2.18)	0.60 (0.04, 2.29)
Age at MPH exposure (yr)	8.00 (7.00, 9.00)	8.00 (7.00, 9.00)
Age at ADHD diagnosis (yr)	8.00 (7.00, 9.00)	8.00 (7.00, 9.00)
Age at MDD diagnosis (yr)	12.00 (9.00, 14.00)	12.00 (9.00, 14.00)
No. of outpatient visit (n)	155.00 (110.00, 222.00)	168.00 (115.00, 229.00)
No. of psychiatric outpatient visit (n)	59.00 (29.00, 95.00)	62.00 (33.00, 101.00)
MPH prescription duration at each visit	25.39 (16.80, 33.43)	25.84 (16.89, 33.45)
Antidepressant use (d)	107.00 (42.00, 280.00)	112.00 (42.00, 317.00)

Values are presented as number (%) or median (interquartile range).
MPH, methylphenidate; MDD, major depressive disorder; ADHD, Attention Deficit Hyperactivity Disorder.

Table 4. Self-controlled case series analyses of subgroup

Risk period	MPH start within 3 years after ADHD diagnosis			MPH start within 1 years after ADHD diagnosis		
	No. of events	IRR (95% CI)	p value	No. of events	IRR (95% CI)	p value
Total						
Unexposed	1,701	1		1,474	1	
Pre exposed: 90 d	104	11.7 (9.5−14.42)	< 0.001	87	12.41 (9.87−15.6)	< 0.001
Exposed	3,492	19.37 (17.77−21.11)	< 0.001	2,781	20.93 (19.02−23.03)	< 0.001
After exposed: 30 d	41	2.78 (2.04−3.81)	< 0.001	36	3.09 (2.21−4.32)	< 0.001
After exposed: 31−60 d	17	1.21 (0.75−1.95)	0.439	15	1.35 (0.81−2.25)	0.253
After exposed: 61−90 d	26	1.93 (1.3−2.84)	< 0.001	20	1.87 (1.2−2.92)	0.006
Age		1.58 (1.56−1.61)	< 0.001		1.62 (1.6−1.65)	< 0.001
Age 6 to 9 years						
Unexposed	447	1		351	1	
Pre exposed: 90 d	32	11.91 (8.19−17.31)	< 0.001	22	12.07 (7.7−18.91)	< 0.001
Exposed	1,777	17.21 (14.99−19.75)	< 0.001	1,328	18.5 (15.78−21.68)	< 0.001
After exposed: 30 d	11	1.72 (0.94−3.14)	0.079	9	1.81 (0.93−3.53)	0.082
After exposed: 31−60 d	4	0.69 (0.26−1.86)	0.464	3	0.67 (0.21−2.1)	0.493
After exposed: 61−90 d	9	1.7 (0.88−3.3)	0.117	8	1.96 (0.97−3.98)	0.061
Age		1.53 (1.5−1.56)	< 0.001		1.58 (1.54−1.62)	< 0.001

CI, confidence interval; MPH, methylphenidate; ADHD, Attention Deficit Hyperactivity Disorder.

ilar pattern to the overall analysis (Table 4). Further analysis revealed that an increased risk of depression was detected during the 90-day period before methylphenidate initiation (IRR: 11.7; 95% CI: 9.5−14.42). The risk remained elevated during the methylphenidate exposure (IRR: 19.37; 95% CI: 17.77−21.11) and after MPH treatment discontinuation, the IRR decreased for the first 30 days (IRR: 2.78; 95% CI: 2.04−3.81, $p < 0.001$) and then returned to baseline levels by 31 to 60 days after MPH treatment discontinuation (IRR: 1.21; 95% CI: 0.75−1.95, $p = 0.439$). During the period from 61 to 90 days after MPH treatment discontinuation, the IRR slightly increased (IRR: 1.93; 95% CI: 1.3−2.84, $p < 0.001$). In the young age group, the IRR increased in the 90 days before MPH exposure (IRR: 11.91; 95% CI: 8.19−17.31, $p < 0.001$). After prescription of MPH, the IRR was 17.21 (95% CI: 14.99−19.75, $p < 0.001$), and it returned to baseline levels by 1 to 30 days after MPH treatment discontinuation (IRR: 1.72; 95% CI: 0.94−3.14, $p = 0.079$). Age was associated with an increased risk of MDD (IRR: 1.53; 95% CI: 1.5−1.56, $p < 0.001$). The subgroups of children who were initiated MPH within 1 year after ADHD diagnosis showed a similar pattern to the overall analysis. The IRR during MPH exposure was 20.93 (95% CI: 19.02−23.03, $p < 0.001$) in the total age group and 18.5 (95% CI: 15.78−21.68, $p < 0.001$) in the young age group.

DISCUSSION

This study found a significantly positive temporal association between MDD and MPH treatment in youth with ADHD. To our knowledge, this is the first national population-based self-controlled case series study to focus on the incidence of MDD in children exposed to methylphenidate. In this retrospective population-based study, the incidence of MPH-related MDD was elevated by 12.12-fold and 18.06-fold before the start of MPH treatment and during the exposure period, respectively. After discontinuation of MPH treatment, the incidence of MPH-related MDD returned to baseline within 60 days. This finding suggests that the risk of MDD increases after initiation of MPH treatment, with an increased risk of MDD prior to the start of MPH treatment that begins to fall after discontinuation of MPH. However, the results of this study are contrary to the findings of previous studies, which found that MPH has a protective effect against depression [19,29]. To date, this is the first study to investigate the risk of MDD before and after methylphenidate treatment using an SCCS design. Therefore, our study provides new evidence for the relationship between MPH and depression.

Previous studies presented inconsistent findings on the effect of ADHD medication usage on depression. Our finding that ADHD medication temporally positive associated with depression corroborates reports from clinical studies by Staikova *et al.* [30] and Jensen *et al.* [31] In contrast, Chang *et al.* [19] found a protective effect of ADHD medication on the development of depression and concurrent depression. The contradictory findings are likely to be due to methodological differences. In Chang's study, occurrence of depression was defined in a very restricted manner. For example, the occurrence of depression was observed only for a period of 1 year, and in the analysis of concomitant depression, only unscheduled visits were included as an occurrence of depression during the ADHD medication period. Thus, the incidence of depression might appear to be lower than it actually is, and the risk of depression may also be underestimated.

We found an increased risk of depression before MPH treatment. The most reasonable interpretation of this incidence pattern may be the result of mental health problems, functional impairments, and related factors leading to the medical consultation before deciding on MPH treatment. As another possible explanation, when antidepressants were primarily prescribed to patients with ADHD who developed depression, underlying ADHD symptoms that did not sufficiently improve with antidepressant use may have been highlighted, and MPH may have been added to the treatment regimen. In these cases, regardless of the association between MPH use and the occurrence of depression, the IRR of MDD before MPH treatment appears to increase. After all, the increased MDD IRR before MPH use may reflect antidepressant use in patients with ADHD.

In our study, the increase in the IRR of MDD during the MPH exposure period should be interpreted with caution. The median duration from the start of MPH treatment to depression incidence was 162 days. Since the development of depression takes at least a few weeks, we cannot conclude that an immediate occurrence of depression after MPH administration is due to MPH exposure. However, further studies are needed to investigate the possibility that underlying subthreshold depression is exacerbated by MPH administration. Moreover, anorexia, insomnia, and physical symptoms, which are factors related to depression, may be triggered as side effects of MPH, which may worsen the underlying subthreshold depressive mood.

Prior case reports in which MPH use induced depressive symptoms in children have been published [32,33]. However, in those cases, the depressive symptoms that emerged were interpreted as manifestations of other psychiatric disorders rather than being associated with MPH. In addition, in the classical cohort study, participants with subsyndromal comorbidity were usually excluded at the participant recruitment stage, so there are few published reports of exacerbation of depression caused by MPH usage. In one nationwide prospective cohort study that investigated the effects of MPH on depression, high MPH drug adherence in children was reported as a predictor of antidepressant use in adolescents [34]. However, there is a notable limitation of that study: MPH drug adherence necessarily reflects disease burden, including the burden of comorbid psychiatric disorders, and psychosocial environment. Therefore, in our study, confounding factors were adjusted by using a within-person design to examine the relationship between MPH administration and the risk of depression.

It is noteworthy that the IRR of MDD decreased to baseline levels within approximately 60 days after MPH discontinuation. This contrasts with the observed increase in MDD IRR prior to MPH drug treatment. If we assume that discontinuation of MPH drug treatment reflects the disappearance of the symptoms that led to medical consultation, the reduction in MDD IRR within 60 days after MPH discontinuation can be explained. In contrast, the slight increased MDD IRR during 61 to 90 day after MPH discontinuation may be the result of exacerbation and relapse of symptoms.

The whole group maintained a high IRR compared to baseline within 30 days after drug discontinuation, whereas the group between 6 and 9 years old demonstrated a decrease in MDD IRR immediately after drug discontinuation. The differences between these groups can be explained in two ways. First, the young age group, between the ages of 6 and 9, would have been less vulnerable to depression because they had been exposed to fewer adverse social experiences compared to those in the other age groups. Second, the caregiver initially determines the prescription, medication, and termination of a child's medication; the younger the child, the more dependent they are on the caregiver [35].

In our study, the absolute risk of MDD in children with

ADHD was lower than the incidence of depression in ADHD patients reported in previous studies [36,37]. This may be due to the stringent outcome criteria used in this study, which were devised by the authors to ensure the high specificity of MDD relative risk estimation. In particular, considering the low prevalence of MDD in the East Asian population [38,39], the incidence reported in this study might be the actual representation in South Korea.

The main strengths of our study are its population-based sample and longitudinal design. Our study included the entire population of Korean children who were diagnosed with ADHD during the study period. Unlike in previous studies, individuals who were prescribed MPH were investigated for a long time period of approximately 9 years following the start of treatment [19]. An additional strength is that we used a self-controlled case study to overcome the limitations of pharmacoepidemiologic observational studies, which tend to increase selection bias. Patients who are prescribed medications after receiving a diagnosis and those who are not treated may differ in various areas, such as disease severity, comorbidities, environmental resources, and attitudes toward medication. There is a risk of selection bias since information about these confounders cannot be obtained from most sets of population-based data. Therefore, SCCS is an effective study design that overcomes such limitations of previous studies.

Our findings should be considered in the context of other limitations. First, data on drug compliance are not captured in claims data. Subjects may not use MPH as prescribed. Second, we had no information before January 1, 2007. Our results are strengthened by the additional subgroup analyses done on patients between the ages of 6 and 9, who were relatively young and less likely to develop depression. Another discrepancy may be variations in diagnoses among physicians, who inevitably vary in the procedures they employ and the treatments they prescribe for any given type of medical condition. Third, the presence of depression and ADHD was identified by diagnostic code from an medical claims database and therefore, bias might occur due to the misclassification or inaccurate registration. Further limitations of our study include an absence of information on MPH dosage, missed doses, and the possibility that milder depression would not result in clinic visits and might thus have been missed. Finally, we focused on depression associated with MPH treatment, but we did not assess the use of concomitant medications, some of which are known to cause depression [40].

Our findings suggest that use of methylphenidate medication in young people with ADHD is temporally associated with the emergence of depression. With the increased global use of ADHD drugs, the benefits of methylphenidate should be carefully evaluated against the potential risk of depression in children and adolescents.

■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Conceptualization: Yunhye Oh, Yoo-Sook Joung, Jinseob Kim. Formal analysis: Yunhye Oh, Yoo-Sook Joung, Jinseob Kim. Funding acquisition: Yunhye Oh. Methodology: Yunhye Oh, Yoo-Sook Joung, Jinseob Kim. Writing—original draft: Yunhye Oh, Yoo-Sook Joung. Supervision: Yoo-Sook Joung.

■ **ORCID**

Yunhye Oh https://orcid.org/0000-0002-5945-2621
Yoo-Sook Joung https://orcid.org/0000-0002-9225-4643
Jinseob Kim https://orcid.org/0000-0002-9403-605X

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